THE

AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JUNE, 1941

ORIGINAL ARTICLES.

POSSIBLE ADAPTATION TO A LOW VITAMIN B_1 INTAKE.*

By F. M. Meyers, M.D.,

MEDICAL DIRECTOR, PETOEMBOEKAN, EAST COAST OF SUMATRA, NETHERLANDS EAST INDIES.

(From the Hospital of the "Serdang Dokter Fonds.")

The Netherlands East Indies seem to be a suitable place for the study of subclinical vitamin B_1 deficiencies on historical grounds, as well as from the point of view of the number of cases. Beriberi appears regularly in these countries, although even if not everywhere of equally frequent distribution. Thus one would expect that the subclinical form of the disease would belong to the daily bread of the medical practitioner. This is not so. The chapters on beriberi in the classical textbooks of tropical diseases are, in their absence of descriptions about conditions of pre-beriberi, illustrative of this fact that seems strange at first sight. Very little therein is said about vitamin B_1 deficiencies *sine* beriberi and not even all authors describe the appearance of constipation as an introductory symptom of the disease. The conception of a subclinical vitamin B_1 deficiency has its origin in some of the temperate parts of the world, chiefly in the United States, and the present writer is confident that many practitioners in the tropics must have been much astonished at the long list of symptoms which, according to Williams and Spies,[15] may be attributed to this condition.

Meanwhile I have elsewhere formulated the suggestion that subclinical pellagra might be held partly responsible for these symptoms;[8] and pellagra is very seldom seen in the Netherlands East Indies.

Since the quantitative estimation of thiamin in blood and urine became possible, a more concrete and less subjective way was given

* At the author's suggestion, this article is being published without submission to him for corrections, in view of present uncertainties of postal communications.—Editors.

to investigate the possible significance of subclinical beriberi for these countries also.

In 15 healthy estate laborers, all men, on a standarized diet containing 1.5 to 2 mg. thiamin daily, the output of thiamin in the urine has been estimated during 1 to 3 consecutive days; in 14 of these test persons, subcutaneous test doses of 2 to 4 mg. daily were given in addition, for 2 or 3 days. No exact information was available as to the thiamin content of the diets before the test period. However, even a superficial knowledge of the feeding habits of the population involved gives every reason to assume that the last mentioned diets will have contained considerably less thiamin as compared with those of the test period; probably between 0.6 to 1 mg. *per diem*.[13b] It may be stated further that the carbohydrate-fat-calorie ratio of the normal diet of the group under consideration is not very favorable in relation to the quantity of thiamin necessary to avoid a deficiency. These diets contain a very high amount of carbohydrate (rice, nowadays very often mechanically polished to a high degree), with low amounts of proteins and fats. That same ratio was contained in the standard diet also: unpolished rice 500 gm., coconut oil 5 gm., dried salted fish 60 gm., and green vegetables 50 gm.

The thiamin outputs could be compared with those of 6 control cases. Three of these, all Chinese, had a mild form of beriberi. The other 3, healthy Javanese, had been prepared beforehand with a diet rich in vitamin B_1, which contained from 2.5 to 3 mg. thiamin and in which the amount of fat was raised to 20 to 25 gm. daily by the addition of 15 gm. red palm oil. This preparatory period had lasted 17, 8 and 10 days respectively.

The output of thiamin* was estimated from the amount in 150 cc. of the assembled 24-hour urine, with the thiochrom method of Westenbrink and Goudsmit.[14]

The results are given in the accompanying table. They give rise to the following conclusions: in the healthy test persons the daily output of thiamin was found to be from 0 to 63 micrograms. Eight times, in 5 persons, no thiamin was found at all. The percentages of the subcutaneous test doses excreted were found to be from 2% to 50%, mostly 10% to 30%, corrections having been made by subtraction of the spontaneous outputs. The highest percentages occurred in all but 1 (Protocol No. 8) of the individuals, who showed a relatively high spontaneous output also. However it must be stated that this correlation, on the whole, was not very definite.

In general, the spontaneous output of thiamin was considerably lower than in investigations from the temperate parts of the world, where figures are given that fluctuate between 40 and 300 micro-

* The thiamin was absorbed with frankonite locally. The absorbates were sent by airmail to the Eykman Institute in Batavia, Java, where the estimations proper were made, through the kind coöperation of Dr. A. G. van Veen.

grams,[2,6,7,10,12,14] although it must be said that absence of any thiamin output also has been encountered there.[2,7,11] Thus our own figures are highly suggestive of a low vitamin B_1 level in the body. Notwithstanding this low level, the fractions of the test doses excreted are well in accordance with those encountered in Europe and the United States. One is inclined to think that the low level of the vitamin in the body in this country seems to result in approximately the same degree of "saturation" as the higher level from elsewhere.

TABLE 1.—THIAMIN EXCRETION PER DIEM.

No. of protocol.	Spontaneous excretion (in micrograms). Days.			Average (in micrograms).	Excretion of test doses in % Days.			Excretion after test doses (In micrograms.) Days.		Of sum of test doses in %	
	1.	2.	3.		1.	2.	3.	1.	2.		
					Healthy unprepared persons.						Thiamin.
1	53	—	—	—	32	50	47.5	233	—	3.0	3 x 2 mg.
2	7	—	—	—	11	14	—	13	—	0.1	2 x 2 "
3	13	—	—	—	16	15	18	20	—	0.1	3 x 2 "
4	0	—	—	—	3	2	—	0	—	0	2 x 2 "
5	19	—	—	—	16	36	33	158	—	2.3	3 x 2 "
6	8.5	39	43	30	17	23.5	—	123	87	1.2	2 x 4 "
7	0	0	—	0	11.5	20	—	177	213	6.4	2 x 4 "*
8	50	13	53	39	12.5	23	24.5	230	153	2.5	3 x 4 "
9	0	17	0	6	18	25	26	327	163	4.0	3 x 4 "
13	41	27	30	33	31	36.5	43	160	97	1.6	3 x 4 "
14	0	0	13	4	17	16	23	60	70	1.0	3 x 4 "
15	47	23	—	35	—	—	—	—	—	—	None
17	7	17	0	8	15	32	28	237	140	3.0	3 x 4 "
18	27	20	40	29			3	6%			1 x 12 " †
19	47	63	57	56			50	0%			1 x 15 " ‡
					Healthy prepared persons.						
12	73	67	80	73	25	29	28	203	180	2.0	3 x 4 " ¶
20	60	57	57	58	30.5	42	38	227	280	3.3	3 x 4 " §
21	0	10	33	14	14.5	5	21	147	110	2.0	3 x 4 "**
					Cases of mild beriberi.						
10	3	0	—	1.5	11	7.5	3	0	133	1.0	33 x 4 "
11	0	170	0	57	4	5	17	63	80	0.3	3 x 4 "
16	0	0	0	0	11.5	2.5	27	60	0	1.5	3 x 4 "

* Thirty-third day after last test dose, output was 123 micrograms.
† Excretion measured during 4 days.
‡ Excretion measured during 5 days.
¶ Diet rich in vitamin B_1 during 20 days.
§ Diet rich in vitamin B_1 during 11 days.
** Diet rich in vitamin B_1 during 13 days.

This point of view receives confirmation from the results in 2 of the prepared control persons. Protocols Nos. 12 and 20 show outputs which are only slightly more than the others and with test dose excretions that are in accordance with the higher ones in the

unprepared individuals. No. 21, however, forms an exception, fully obscure in its cause, whose values approach those of the 3 beriberi cases. This case provides a warning and should prevent too definite interpretations of investigations of this kind. The significance of such exceptions is emphasized by Sciclounoff[11] in Europe and in this country by Pannekoek and van Veen[9] in studies on the vitamin B_1 level in the blood. Melnick and coworkers[7] admit that a low spontaneous output, from 0 to 60 micrograms, may occur in healthy individuals, but on condition that their diets have been very deficient in vitamin B_1, during and only shortly before the test period. According to these investigators, the fraction of extra test doses excreted will then be found to be from 10% to 20%. With excreted fractions of less than 10%, the test person would be more or less deficient. Their results, however, do not agree either with the clinical condition of our own test persons, or with the vitamin B_1 content of the diets used.

Now it cannot be emphasized too strongly that a low vitamin B_1 level of the body should not be confused with a deficiency in the clinical sense of the word, so long as a definite parallel is not established between the two. Elsewhere[8] I have given the description of a *clinical* test for tracing conditions of subclinical vitamin B_1 deficiencies in individuals who seem to be in perfectly good health. This test is based on the fact that the rise in systolic blood pressure, which occurs after an injection of epinephrine, becomes much greater after the test person has been first prepared with thiamin, but only in cases that are deficient. With this test a condition of deficiency could be disclosed in the 3 beriberi cases, in the test persons 2, 7 and 14 of the unprepared individuals, but in none of the 3 prepared control persons. A comparison of these results with the thiamin values shows clearly that a definite correlation between the two does not exist and that a low thiamin level does not mean necessarily the existence of a deficiency.

The fact remains significant, of course, that the spontaneous outputs in our small series were considerably lower as compared with the average of the observations from other parts of the world. The reason cannot be other than a lower vitamin B_1 level of the body in our Javanese. This low level in turn must be the outcome, either from a lower intake, or from a lower storage capacity of the body. Now van Coevorden,[12] in Jansen's laboratory, has established exactly that the individuals with a low intake present a lessened capacity to store the vitamin.

The modern feeding habits of many races in the Netherlands East Indies make a low vitamin B_1 intake very probable.[13b] As has been stated before, the carbohydrate-fat-calorie ratio is not very favorable either. As a rule the inhabitants do not acquire beriberi on these diets. Even conditions of subclinical beriberi are seen much less frequently than one would expect. Van Veen[13a] thinks that an intake of not more than 0.6 mg. thiamin prevents the appearance of

the disease with certainty. On the other hand, it should be mentioned that 4 of the 5 test persons of Jolliffe and coworkers[4] acquired objective as well as subjective symptoms of a deficiency in less than 14 days, after the vitamin had been reduced in their diets from 2.5 to 0.5 mg.

All this suggests the consideration of a possible adaptation to a long-standing low vitamin B_1 intake. Anna Lánczos[5] claims that she has already produced such an adaptation experimentally in hens. A confirmation of her experiments seems highly desirable and of great importance. In human lesions, too, Fabry[1] who works in French Indochina has said, as far back as 1934, that "a great number of persons have only the inapparent form of beriberi" in which "the body installs itself in its dystrophy and lives with it."

If this point of view could be confirmed more definitely as it was possible in the outline given above, this would certainly open wider fields of investigation.

Summary. In a small series of healthy Javanese test persons, under standard conditions, thiamin outputs were found that are considerably lower than the average found in the more temperate parts of the world.

The daily output of thiamin in the population here concerned often does not produce figures that are sufficiently unequivocal to judge, whether in individual cases a condition of deficiency is present or not.

A low vitamin B_1 level of the body should not, without further evidence, be associated directly with a deficiency in the clinical sense of the word.

The vitamin B_1 intake of the population under consideration is very probably much less than the average intake in other parts of the world and on a level which may produce clinical symptoms of deficiency in white people, under experimental conditions.

It is suggested that a chronic low vitamin B_1 intake produces an adaptation of the body.

My thanks are due to Dr. A. G. van Veen, head of the Chemical Department of the Eykman Institute in Batavia (Java), and his staff, for friendly coöperation in this study.

REFERENCES.

(1.) **Fabry**: Trans. IX Congress, Far Eastern Assn. Trop. Med., **2**, 421, 1934. (2.) **Harris, L. J., Leong, P. C.**, and **Ungley, C. C.**: Lancet, **1**, 539, 1938. (3.) **Hou, H. C.**: Trans. X Congress, Far Eastern Assn. Trop. Med., **1**, 529, 1938. (4.) **Jolliffe, N., Goodhart, R., Gennis, J.**, and **Cline, J. K.**: Am. J. Med. Sci., **198**, 198, 1939. (5.) **Lánczos, A.**: Klin. Wchnschr., **18**, 244, 1939. (6.) **Magyar, S.**: Ibid., p. 1157. (7.) **Melnick, D., Field, H.**, and **Robinson, W. D.**: J. Nutr., **18**, 539, 1939. (8.) **Meyers, F. M.**: Geneesk. Tijdschr. Ned. Ind., **80**, 1727, 1940. (9.) **Pannekoek-Westenburg, S. J. E.**, and **van Veen, A. G.**: Ibid., p. 1774. (10.) **Robinson, W. D., Melnick, D.**, and **Field, H.**: J. Clin. Invest., **19**, 399, 1940. (11.) **Sciclounoff, F.**: Schweiz. med. Wchnschr., **69**, 655, 1939. (12.) **van Coevorden, J. S.**: Het opsporen van aneurine (vitamine B_1) tekorten en het voorkomen daarvan by zwangeren, Dissertatie, Amsterdam, 1939. (13.) **van Veen, A. G.**: (*a*) Geneesk. tijdschr. v. Nederl.-Indië, **75**, 2050, 1935; (*b*) Ibid., **80**, 1696, 1940. (14.) **Westenbrink, H. G. K.**, and **Goudsmit, J.**: Nederl. Tijdschr. Geneesk., **3**, 4056, 1937; **1**, 1076, 1938. (15.) **Williams, R. R.**, and **Spies, T. D.**: Vitamin B_1 and Its Use in Medicine, New York, The Macmillan Company, p. 8, 1938.

THE RESPONSE OF BLOOD DONORS TO IRON.

By Albert C. Santy, M.D.,

CLINICAL ASSISTANT, BELLEVUE HOSPITAL AND ROOSEVELT HOSPITAL (MEDICAL CLINIC) NEW YORK, N. Y.

Although occasional blood-letting is sometimes beneficial and is rarely deleterious, frequent donations inevitably cause anemia in the donor. Snapper, Liu, Chung and Yu[10] observed that this anemia was of the hypochromic microcytic type and reported that it responded strikingly to iron therapy, whereas hemoglobin regeneration was uncertain in anemic donors not receiving iron.

In view of the fact that the rapidity of hemoglobin regeneration is of paramount importance to the professional donor and sometimes to the recipient as well, it is curious that the routine administration of iron to donors is not more widespread. It therefore seemed interesting to evaluate iron therapy as applied to repeated blood loss through donation. The present report gives the results of alternate administration and withdrawal of iron to a group of professional donors* during the spring and summer of 1937.

Material and Methods. Reliability in coöperation was regarded as the most important prerequisite in selecting the group for the study. Since the donors were fully aware that a satisfactory hemoglobin level was essential for donations, and that such a level was presumably best maintained by taking iron, it was often difficult to prevent unreliable donors from indulging in self-medication during the control periods. The group was further restricted to include only those men who had at least one course of iron, who gave at least two donations and whose records were followed for at least 5 weeks. There were 27 white male donors in this group. All were healthy and fairly intelligent. With the exception of three clerks and one barber, all were mechanics, laborers, or factory workers. They ranged in age from 22 to 49, averaging 34. The experiment was continued for 16 weeks, but the average time of study for the entire group was only 12 weeks.

Iron was usually administered when the hemoglobin was low and withdrawn when a satisfactory response had been obtained. The form of iron used was exsiccated ferrous sulphate in 3 gr. tablets† (corresponding roughly to 5 gr. U.S.P.). The usual dose was 4 tablets a day. The experience of the agency had shown that this form of iron was most satisfactory for blood donors because of its convenience, effectiveness and freedom from unpleasant gastro-intestinal reactions.

The routine of the agency was not altered except for the systematic administration and withdrawal of iron and the insistence on unusually frequent check-ups. Hemoglobin was read by the acid hematin method, using a standardized Hellige wedge type hemometer.

Results. The subjective response to iron was striking. Most of the donors felt better generally and had better appetite while receiving it. A gain of weight was noted in a few instances. No gastro-intestinal upset was reported.

* The Mixon Blood Donor Agency of Brooklin, N. Y., coöperated for this study.

† Feosol supplied by Smith, Kline & French Laboratories.

Table 1 shows the variations in donations and medication.

TABLE 1.—DETAILS OF FERROUS SULPHATE DONATION.

	Range.	Average.
Number of donations per donor	2–10	4
Number of weeks per donor	5–16	12
Total blood given per donor	500–4150 cc.	1580 cc.
Weekly average per donor	45–343 cc.	132 cc.
Proportion of time on iron therapy	13–80%	50%

The administration of iron was regularly followed by a rise in hemoglobin. One donor had never had a hemoglobin reading of more than 12 gm. per 100 cc., but had 14 gm. per 100 cc. after the first 2 weeks of therapy. During the next 6 weeks on iron he gave a liter of blood in 3 donations, in spite of which his hemoglobin rose to 14.8 gm. In 2 cases there was little or no response to the routine dose of iron, but there was a satisfactory rise of hemoglobin when it was increased to 2 3-gr. tablets t.i.d. There was regularly a depression of hemoglobin immediately after donations. Although this was often followed by stimulation, the return to the original level was usually prolonged if iron was not given.

The hemoglobin curves of 4 typical cases are given in Chart 1.

After 19 donations (500 cc.) which occurred during iron therapy, and subsequent to which iron medication was continued without additional donations, hemoglobin returned to the previous level in an average of 11 days. In 7 similar donations occurring shortly before or after the withdrawal of iron, regeneration was also satisfactory. However, in 5 such donations not immediately preceded or followed by iron therapy, regeneration was much slower. In 2 of these latter cases, the hemoglobin returned to the previous level in 17 and 19 days respectively, but in the other 3 it was still 1.6 to 3 gm. per 100 cc. below the previous level 2 to 4 weeks later, at which time iron was given.

The per cent per day hemoglobin change is shown in Chart 2. This was determined by dividing the percentage hemoglobin change (15.6 gm. = 100%) by the number of days. The calculation was based on all periods where there were hemoglobin readings at intervals of approximately 1 week and where there were no donations or any change of regimen. The range was from +0.2% to +1.3% per day (with an average of 0.67%) during iron therapy, and from −1.7% to +1.6% (averaging +0.08%) without iron. The figure of +1.6% is from the chart of a donor whose hemoglobin level rose immediately after iron was withdrawn, which might indicate delayed response. The average data show that hemoglobin was regenerated 8 times as quickly when the donors were receiving iron.

Physical characteristics of the donors seemed to have little or no effect on the hemoglobin response to iron.

Mean corpuscular hemoglobin and reticulocyte counts tended to

rise and fall with the hemoglobin curves. The increase of reticulocytes was never marked, even after donations or during iron therapy. At such times the average was only about 2%, and in no case did the count exceed 3%.

There was little variation in white blood counts.

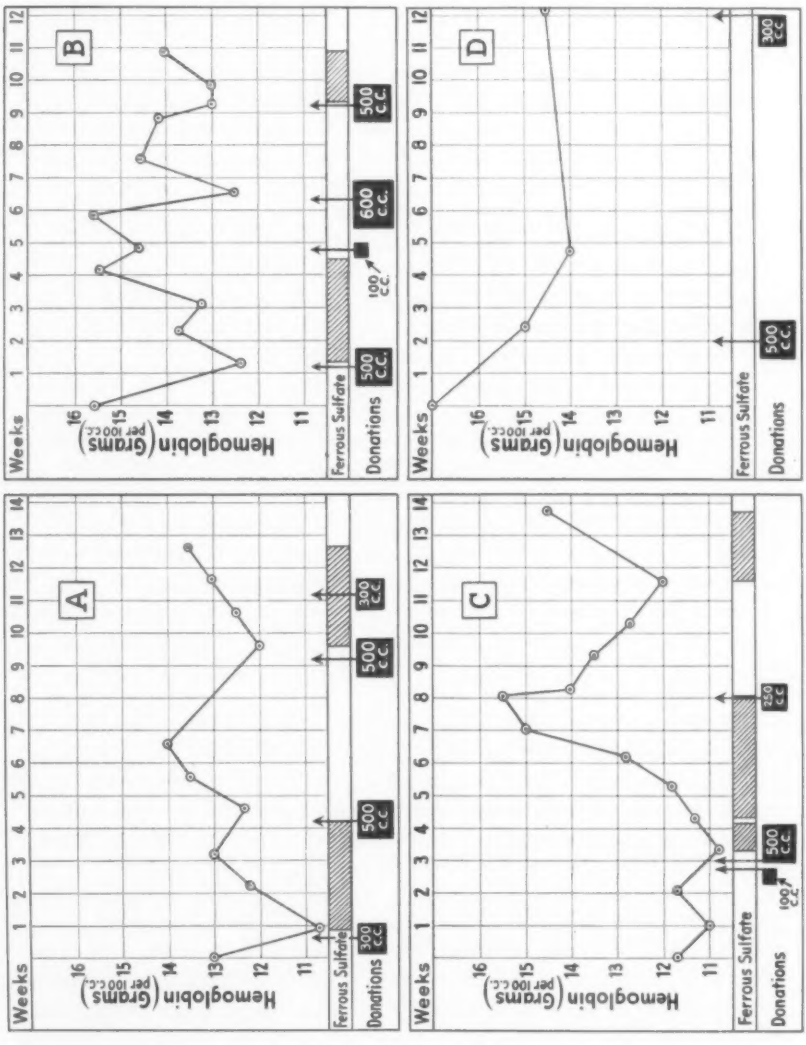
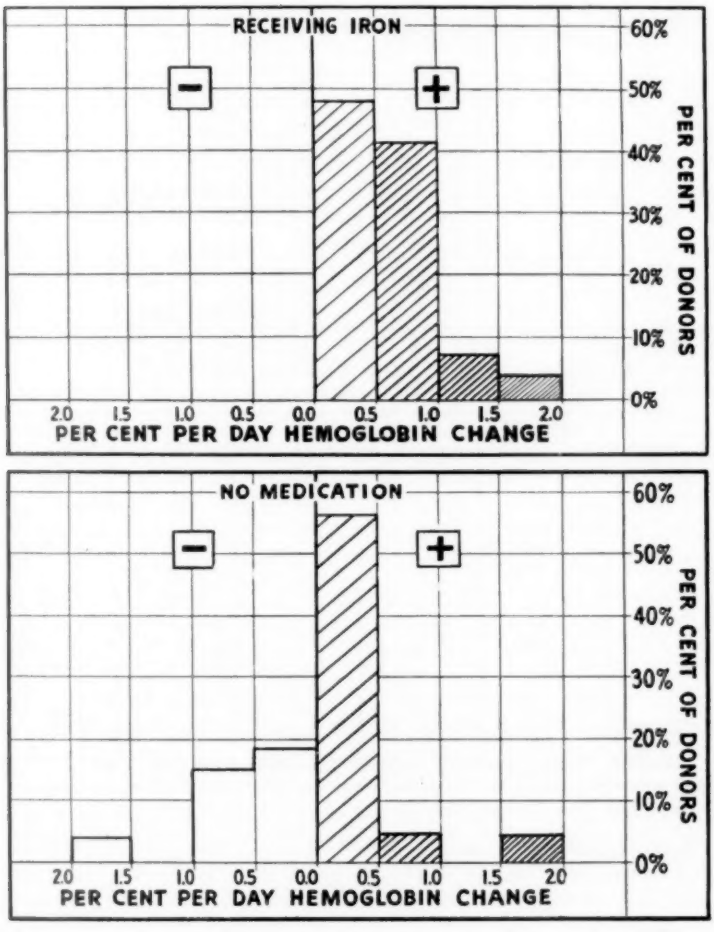


CHART 1.—HEMOGLOBIN CURVES OF 4 TYPICAL CASES.

A–B, Cases showing hemoglobin response during iron therapy and continuing after withdrawal. The protracted effect could be ascribed to hematopoietic stimulation from donations as well as to reserves of tissue iron. *C*, Case showing hemoglobin response to iron, but ceasing when it was withdrawn. *D*, Case showing the slower hemoglobin regeneration without iron medication.

It was of interest to compare the total amount of hemoglobin in the circulating blood with and without iron. The hemoglobin change (in grams per 100 cc.) during the entire periods was multiplied by blood volume in cc. according to Gibson and Evans' table[2] and divided by 100. To this was added the amount of hemoglobin

CHART 2.—PER CENT PER DAY HEMOGLOBIN CHANGE IN 27 DONORS IN PERIODS DURING WHICH NO DONATIONS OCCURRED.

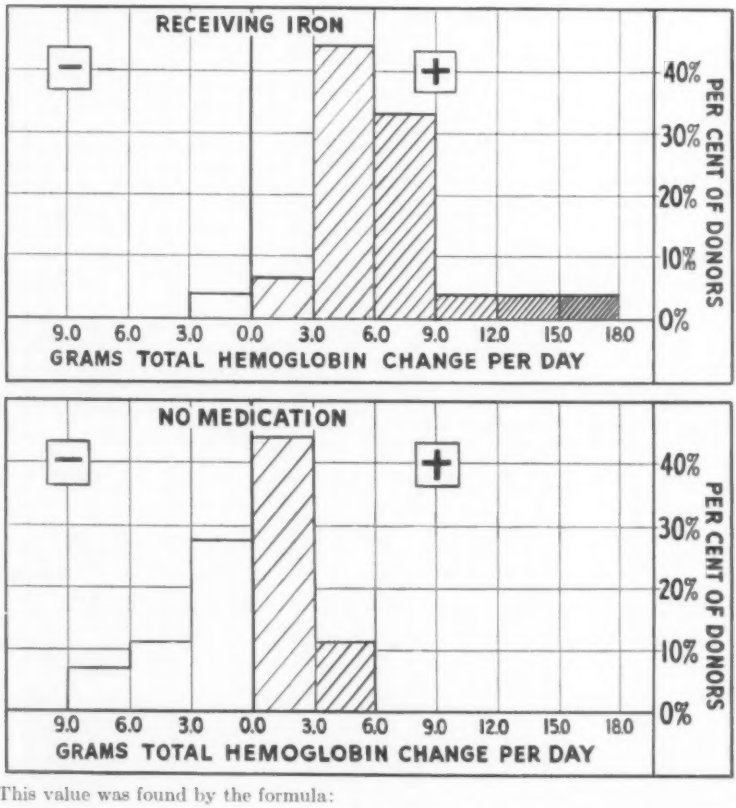


in donations (found by multiplying the number of cubic centimeters of blood given by the previous hemoglobin reading and dividing by 100). The sum of these was divided by the number of days in the periods, giving the average daily rise or fall in the total amount of hemoglobin in the entire circulation. Although these calculations are based on figures which are necessarily subject to considerable

CHART 1.—HEMOGLOBIN CURVES OF 4 TYPICAL CASES.

error, the difference between the negative balance found when iron was not given and the markedly positive balance in the periods of iron medication is sufficiently striking to be significant (Chart 3). The range of variation was from −1.66 to +13.8 gm. per day (with an average of 5.8) during iron therapy, and from −8.25 to +4.77 gm. per day (averaging −0.16) in periods without medica-

CHART 3.—TOTAL HEMOGLOBIN CHANGE PER DAY IN 27 DONORS.



This value was found by the formula:

$$\frac{\text{Hb. change in gm. per 100 cc.} \times \frac{\text{blood vol.}}{100} \quad \frac{\text{donations in cc.} \times \text{Hb. in gm. per 100 cc.}}{100}}{\text{Number of days}}$$

tion. There was only one negative figure during medication. This was observed in a donor showing an initial rise of 1.5 gm. hemoglobin per 100 cc. in the first 2 weeks of iron therapy but a drop of 2.5 gm. per 100 cc. in the next 3, during which period 2 donations were given. Following withdrawal of iron, the hemoglobin increased 4 gm. per 100 cc. in 2 weeks, which seemed attributable to delayed response to iron, hematopoietic stimulation from the dona-

tions, or to both. Similar effects could be suspected in most of the other cases where there was a positive hemoglobin balance during periods without iron.

A study was also made of the hemoglobin balance of 3 donors who had original readings of over 16 gm. per 100 cc. and who were not given iron. One showed a loss of 0.3 gm. total hemoglobin per day over a period of more than 2 months, and the others gained 0.7 and 1.3 gm. per day respectively. The larger of these gains would be sufficient for a donation of 132 cc. once every 17 days, as opposed to the average donation of 132 cc. every week as given by the 27 subjects shown in Table 1, and it would allow for a 500 cc. donation only once in 63 days, as compared to the 11-day period which sufficed for the 19 subjects receiving iron, as stated above.

Comment. In interpreting the results, the complexity of hemoglobin regeneration must be borne in mind. The immediate *apparent* regeneration is probably due to utilization of body stores, as suggested by Hutchison.[5] But this mobilization cannot effect permanent regeneration unless the deficiency is compensated by iron intake.

The hemoglobin regeneration represented in Chart 2 (0.67% per day) is not phenomenal compared to the response that may be expected in severe iron-deficiency anemia. But as Heath[4] states, the results obtained are in inverse proportion to the degree of anemia; and in this series of cases, most of the subjects could not properly be classed as anemic at all. The amount of blood that can be safely withdrawn varies, of course, with the individual. Merklen, Israel and Apffel[9] felt that 100 cc. per month should be the usual limit. This figure agrees with the limit set by Giffin and Haines,[3] but Brewer[1] and Martin and Myers[8] were more conservative. Jones, Widing and Nelson,[6] on the other hand, found no ill-effects from donations of 400 cc. repeated 4 or 5 times at 4- to 5-day intervals.

Since donors receiving iron gained an average of 5.77 gm. of total hemoglobin per day, they could be expected to give 500 cc. at intervals averaging 2 weeks without lowering the hemoglobin level. The negative hemoglobin balance of subjects without benefit of iron (Chart 3) indicates that much longer periods of regeneration are necessary when no medication is given. Although infrequent blood-letting may be beneficial, repeated hemorrhage leads inevitably to a state of anemia unless remedial measures are taken. In view of the fact that the hemoglobin usually continued to rise for some time after iron was withdrawn, the best time to give iron is apparently before rather than after blood loss, in order to supply sufficient stored iron to compensate for the expected fall of the hemoglobin level. When there is frequent repetition of blood loss, or when response to iron is less than average, medication should, of course, be protracted.

As regards the amount of blood loss as well as its periodicity, menstruation is comparable to professional donation. Women who lose but little blood can make up the iron deficiency through ordinary nutrition. But according to Leverton and Roberts'[7] figures, the average iron requirement for menstrual loss is 15 mg. a day, which is more than is found in the average diet. Supplementary iron therapy is therefore indicated for the average menstruating woman as well as for the average regular blood donor.

Summary. The hemoglobin response of 27 active professional blood donors was studied under iron therapy and without medication.

It was found that hemoglobin regeneration after donations took place 8 times more rapidly when iron was given.

The return to the previous level was complete in an average of 11 days after a 500 cc. donation under iron therapy, whereas a far longer period was necessary when iron was withheld.

A rough calculation of the amount of hemoglobin in the total circulation revealed the fact that the average active donor in this series could not maintain a positive balance without iron medication.

It was found that the response to iron usually continued after its withdrawal, indicating that the most effective time to administer iron is before blood loss.

It is concluded that the diet of regular donors should be supplemented with iron. Ferrous sulphate, because of its convenience and freedom from reactions, was regarded as a very satisfactory form of iron for blood donors.

REFERENCES.

(1.) **Brewer, H. F.**: Brit. Med. J., **1**, 895, 1939. (2.) **Gibson, J. G., Jr.**, and **Evans, W. A., Jr.**: J. Clin. Invest., **16**, 317, 1937. (3.) **Giffin, H. Z.**, and **Haines, S. F.**: J. Am. Med. Assn., **81**, 532, 1923. (4.) **Heath, C. W.**: Arch. Int. Med., **51**, 459, 1933. (5.) **Hutchison, J. H.**: Arch. Dis. Child., **12**, 305, 1937. (6.) **Jones, H. W., Widing, H.**, and **Nelson, L.**: J. Am. Med. Assn., **96**, 1297, 1931. (7.) **Leverton, R. W.**, and **Roberts, L. J.**: J. Nutr., **13**, 65, 1937. (8.) **Martin, J. W.**, and **Myers, J. T.**: J. Lab. and Clin. Med., **20**, 593, 1935. (9.) **Merklen, P., Israel, L.**, and **Apffel, A.**: Presse méd., **44**, 1941, 1936. (10.) **Snapper, I., Liu, S. H., Chung, H. L.**, and **Yu, T. F.**: Chinese Med. J., **56**, 403, 1939.

BEE VENOM IN THE TREATMENT OF CHRONIC ARTHRITIS.

By Joseph Lee Hollander, M.D.,

ASSISTANT PHYSICIAN, THE PENNSYLVANIA HOSPITAL, PHILADELPHIA, PA.

Bee stings have been used in the treatment of arthritis for nearly a century. The idea began with an empirical observation that some victims of arthritis were relieved of their pain after accidental encounters with bees, and that bee keepers seldom suffered from rheumatism. Phillip Terc[10] and later other European physicians deliberately exposed patients to stings of the honeybee with reportedly good results (Beck[1]). The idea has become so popular in this country that a bee keeper remarked to the writer that selling

bee stings to rheumatics yielded a better income than the sale of the honey.

Chemically, bee venom is an albumin-free sapotoxin allied to snake venom combined with a poison similar to cantharides (Hench, *et al.*[5]). It contains some histamine, but no formic acid. The therapeutic action depends on a foreign protein reaction (Kroner[6]), a counter-irritation, or a histamine-producing action (Beck[1]).

The assumption that arthritis results from impaired circulation of blood and lymph in the joint tissues leading to accumulation of lactic acid and permitting bacterial growth, forms the basis of the rationale of this treatment (Beck). Bee venom has a vasodilating action thus increasing local blood supply and tending to correct the basic fault.

Several forms of bee venom for injection have been produced to facilitate the regulation of the dosage, and eliminate the obvious objections to direct bee stings. Apicosan, Apicur, Ven-apis, and Lyovac Bee Venom are examples of bee venom solutions.

Many European investigators have employed bee venom in the treatment of chronic arthritis and report good results (Sauerwald,[9] Thompson[11]). American reports are fewer and a little less optimistic. Kroner and his co-workers[6] treated a series of 100 cases of atrophic arthritis, but used no controls. These investigators reported no cures, but 35 patients were markedly improved, 38 were moderately improved, or, in all, 73 patients were improved by the treatment. Relief from pain was reported to be definite and lasting, and a decreased erythocyte sedimentation rate was noted. In a later paper one of the co-authors (Nicholls[7]) reported discouraging results in 27 patients treated with actual bee stings.

Burt[2] analyzed the results in 50 of his series of 200 cases in which bee venom in solution was employed. Sixteen were "much better," 9 were "better," 15 were unchanged, and 10 patients were worse after the treatment. He concluded that bee venom therapy is by no means specific but of definite value in some cases. Other reports, such as those of Douthwaite[4] and Reichart,[8] are more skeptical of the virtues of bee venom in the therapy of arthritis.

The present study was undertaken to evaluate the benefit from bee venom in solution in the treatment of arthritis in a controlled series of cases. Fifty-nine patients suffering from rheumatic diseases, 38 of whom were female and 21 were male, were taken at random from the arthritis clinic and wards of the Pennsylvania Hospital. The age of the patients ranged from 23 to 69 years, and the duration of the disease from 5 months to 33 years. All the patients were examined and obvious foci of infection eliminated before treatment was begun. The prescribed diet was low in carbohydrate, high in vitamins, and of adequate caloric value for each patient. No treatment except the injections of bee venom in solution was given during the period of observation.

Since the psychic benefit from any vigorous form of therapy in chronic illness was appreciated, 17 patients were included in a control group. In this group there were 9 cases of atrophic arthritis, 7 of hypertrophic arthritis, and one of mixed arthritis. These patients were given injections of a mild non-specific protein solution.

Forty-two patients were treated with bee venom in solution. Twenty-four of these had atrophic arthritis, 10 had hypertrophic arthritis, and 6 had the mixed form. One case of rheumatoid spondylitis, and one of severe chronic fibrositis were included.

Determinations of erythrocyte sedimentation time and Schilling differential leukocyte counts were routinely carried out before and after the course of treatment on all patients. These two tests help to indicate the activity of the rheumatic disease.

Method. Two brands of bee venom solution were used in the study. Ven-apis, a solution of bee venom, was supplied in 3 concentrations to facilitate increasing dosage. "Lyovac" Bee Venom, a powdered form, was supplied with ampoules of normal saline so that injections could be given immediately after dissolving the venom to prevent inactivation. Ven-apis was used in the first 22 cases, and the "Lyovac" Bee Venom in the last 20. Since results from the two preparations were closely parallel, no distinction will be made between the groups.

Injections were given usually over the extensor surface of the most painful joints. The skin was prepared with acetone, as alcohol inactivates the venom. A small initial test dose was injected to detect the degree of sensitivity. The venom solution was given in intracutaneous wheals containing 0.1 cc. each, and spaced 1 to 2 cm. apart.

The number of wheals was increased twice a week until the patient received the equivalent of 10 to 30 bee stings per visit. The amount given was determined by the individual reaction to the solution.

Only patients treated more than 6 times were included in the series. Most of the patients were injected 20 times or more, or received the equivalent of more than 100 bee stings.

Each of the patients in the control group was given 15 injections of Proteolac, a milk protein solution, intramuscularly or intravenously, at weekly intervals.

Results. Of the 42 patients with chronic arthritis treated with bee venom solution none was completely relieved of his disease. Three patients were markedly improved, 5 more were moderately but perceptibly better, and 9 experienced some relief during the course of treatment but relapsed soon after the injections were discontinued. Twenty-two patients were unaffected by bee venom therapy, and 3 were definitely worse after treatment.

In the control* cases treated with Proteolac, 3 were perceptibly improved, 5 more were better while receiving injections but they obtained no lasting benefit; and the condition of the remaining 9

* The word "control" must here be accepted with reservations, as "control" would, strictly speaking, require the use of a therapeutically inert material, not one that produces non-specific protein shock. It must be kept in mind that non-specific protein reaction may at times be helpful in arthritis and that the effect of bee sting itself may be in part on such a non-specific protein reaction basis.—Editors.

patients was unchanged. No untoward reactions occurred in these cases.

Decreased pain and stiffness in the joints, increased appetite and increased strength were subjective signs of improvement. Objectively, the criteria were: decreased swelling and increased mobility of the joints involved, gain in weight, increased hemoglobin and red blood cells, a decreased number of immature neutrophils in the blood count, and a decreased erythrocyte sedimentation rate.

The length of treatment and actual number of injections did not have a direct effect on the degree of improvement. In the patients showing lasting benefit from bee venom treatment the average number of visits was 18, with improvement showing itself as early as the third week.

In the unimproved group, the average number of treatments was 21, with one patient experiencing no change after 32 injections. The patients made worse by the treatments had 8, 9, and 17 injections respectively.

In the 8 patients improved following bee venom therapy the decrease in the corrected erythrocyte sedimentation rate did not closely parallel the actual degree of improvement felt by the patient, but in 6 a decrease of more than 6 mm. was found. The filamented-non-filamented neutrophil ratio did not closely follow the degree of apparent benefit from treatment, but shifts toward normal were noted in 7 instances. A few of the unimproved patients showed improvement in sedimentation rate, but the change was always only a few millimeters.

TABLE 1.—RESULTS IN 42 CASES OF ARTHRITIS TREATED WITH BEE VENOM.

Type of arthritis.	No. of cases.	Greatly improved.	Moderately improved.	Temp. improved.	Unchanged.	Worse.
Atrophic (rheumatoid):						
Advanced	15	1	2	1	9	2
Early	9	1	1	1	5	1
Mixed: advanced	6	0	0	3	3	0
Hypertrophic	10	0	2	4	4	0
Fibrositis	1	1	0	0	0	0
Rheumatoid spondylitis	1	0	0	0	1	0

In Table 1 the 42 cases are subdivided into types of arthritis with results by sub-groups. Table 2 shows results in the control series for comparison.

TABLE 2.—RESULTS IN 17 CASES OF ARTHRITIS TREATED WITH PROTEOLAC.

Type of arthritis.	No. of cases.	Greatly improved.	Moderately improved.	Temp. improved.	Unchanged.	Worse.
Atrophic (rheumatoid):						
Advanced	6	0	1	1	4	0
Early	3	0	1	0	2	0
Mixed	1	0	0	1	0	0
Hypertrophic	7	0	1	3	3	0

Untoward reactions to the injections of bee venom solution were fairly uncommon. In several instances the local reaction was excessive, the wheals showing pseudopod formation, and edema of the area ensued. Little generalized reaction occurred except for mild headache which was occasionally complained of. Symptoms of toxicity developed in 2 patients, necessitating termination of treatment. Both patients had headache, weakness, irritability, and frequency of urination, and definite albuminuria was noted in one.

Discussion. The most marked improvement following bee venom therapy was seen in the case of fibrositis, in which an almost complete remission of symptoms occurred. Reichart[5] and other workers have found that fibrositis is more responsive to bee venom therapy than rheumatoid arthritis. The frequent spontaneous remissions characteristic of chronic fibrositis[3] must be borne in mind in evaluating results, however.

One case of advanced atrophic arthritis showed a definite symptomatic and objective improvement. This woman had been very much discouraged with results from other forms of treatment, but improved definitely with the use of bee venom. Pain, swelling, and stiffness of the diseased joints was decreased, her general health became better, and the blood count and sedimentation rate improved. The good result in the early case of rheumatoid arthritis must be at least partially credited to the removal of diseased tonsils 6 weeks before treatment began.

The course of chronic arthritis is rarely uniform. The victims suffer a series of relapses and partial remissions, perhaps even more disheartening than a steady downward course. The variation in intensity of the arthritis occurs independent of treatment, and makes evaluation of improvement secured from any one form of therapy very difficult. Temporary improvement and subjective benefit should not be regarded with much optimism.

The proportion of patients showing subjective or temporary improvement was about the same in the subdivisions of the treated group, as well as in the control group. This improvement could be attributed to psychic benefit alone.

The most interesting, and perhaps most significant, case was that of J. R. For 23 years this man had suffered from rheumatoid arthritis, and his principal occupation for the past 18 years was keeping bees! He had been stung hundreds of times and he had "sold" bee stings to other arthritics, but still had the complaints and deformities characteristic of advanced atrophic arthritis. This patient was given a course of bee venom injections with no improvement at all. It must be stated, however, that he was actually immune to bee stings, there being no local or general reaction following large doses of venom.

Summary. 1. Forty-two patients with chronic arthritis were treated with an injectable solution of bee venom. Eight patients were improved. Of these, 2 cases of rheumatoid arthritis and one of fibrositis were markedly better.

2. The number of treatments varied from 6 to 32 over periods ranging from 4 weeks to a year. The length of treatment and total dosage showed no apparent correlation with degree of improvement.

3. Seventeen patients were given foreign protein injections, and were regarded as a control group. Three of these patients showed lasting improvement.

4. The incidence and degree of improvement were very discouraging, and all but one of the patients, the one suffering from fibrositis, are still seeking relief from their disease. Even though a few patients showed definite and lasting improvement, it is felt that a painful, tedious, expensive, and somewhat toxic form of therapy should yield much better results to justify its continued use.

REFERENCES.

(1.) **Beck, B. F.**: Bee Venom Therapy. New York, Appleton-Century Company, 1935. (2.) **Burt, J. B.**: Brit. J. Phys. Med., **12**, 171, 1937. (3.) **Comroe, B. I.**: Arthritis. Philadelphia, Lea & Febiger, p. 371, 1940. (4.) **Douthwaite, A. H.**: Survey of Chronic Rheumatic Diseases, London, Oxford University Press, p. 265, 1938. (5.) **Hench, P. S., Bauer, W., Dawson, M. H., Hall, F., Holbrook, W. P., Key, J. A., and McEwen, C.**: Ann. Int. Med., **13**, 1837, 1940. (6.) **Kroner, J., Lintz, R. M., Tyndall, M., Andersen, L.,** and **Nicholls, E. E.**: Ann. Int. Med., **11**, 1077, 1938. (7.) **Nicholls, E. E.**: New York State Med. J., **38**, 1218, 1938. (8.) **Reichart, A.**: Proceedings of International Congress on Rheumatism and Hydrology, London, Headley Brothers, p. 204, 1938. (9.) **Sauerwald, A.**: Deutsch. med. Wchnschr., **60**, 1605, 1934. (10.) **Terc, P.**: Med. Presse, **29**, 1261, 1880. (11.) **Thompson, F.**: Lancet, **2**, 446, 1933.

HEBERDEN'S NODES.*

HEREDITY IN HYPERTROPHIC ARTHRITIS OF THE FINGER JOINTS.

BY ROBERT M. STECHER, M.D.,
CLEVELAND, OHIO.

(From the Department of Medicine of Western Reserve University School of Medicine and the Division of Medicine of City Hospital.)

THE term Heberden's nodes today indicates enlargements of the terminal joints of the fingers due to hypertrophic arthritis, though Heberden himself spoke of hard knobs "particularly a little below the top near the joint." They arouse the patient's interest by the unsightly deformity which results rather than from any severe degree of discomfort or disability which they produce. Alarm is also occasioned because of the fear that they betoken a crippling disease. Such apprehensions are without foundation because, although Heberden's nodes are properly regarded as a manifestation of hypertrophic arthritis, the disease is most often limited to the

* Read at the annual meeting of the American Rheumatism Association in New York City, June 10, 1940.

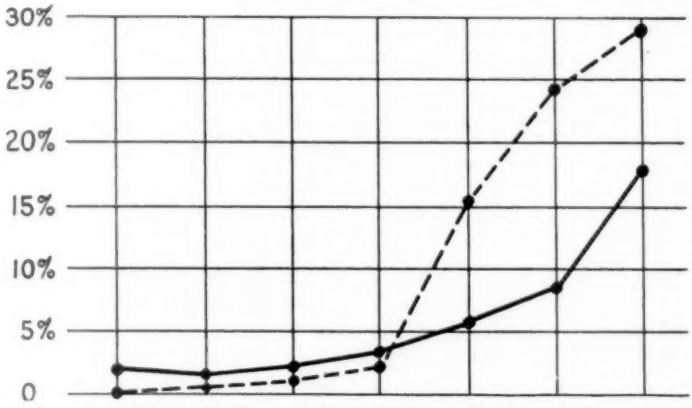
fingers. Many generalizations concerning hypertrophic arthritis are applicable to Heberden's nodes but certain advantages are to be derived from considering this disease as a distinct clinical entity. The purpose of this paper is to present evidence that the occurrence of Heberden's nodes is strongly influenced by heredity.

Despite the benign nature of the disease Heberden's nodes are frequently mentioned in the literature. Their familial nature has been pointed out. Charcot[1] stated, "It is a hereditary disease and may appear in several members of the same family." Duckworth[2] describes a family in which Heberden's nodes occurred in four generations in direct descent affecting mostly the female line but involving 3 brothers and 1 sister of one generation. Wick[5] discovered familial involvement in 6 cases of 100 studied. Monroe[3] states that, "Hereditary influences may be at work in those in whom they appear early in life. Such a familial trait has been reported by the several patients under thirty years of age that I have had."

Heberden's nodes may occur as a result of direct trauma, usually a single episode, severe enough to be distinctly recalled as to time and circumstance. The injury is followed promptly by enlargement which remains constant after several months. These so-called traumatic nodes are common in men and are most often confined to one finger or at least to one hand. Traumatic nodes, when they occurred, have been eliminated from this study because our attention is confined to another form of the disease, idiopathic Heberden's nodes. These arise spontaneously without relation to trauma, starting in one finger but spreading, in a period of several months to several years, to other fingers until all may be affected. A previous study[4] based on observation of nearly 7000 individuals showed that the incidence of both traumatic and idiopathic Heberden's nodes varies with race, sex and age differences. Figure 1 shows the incidence of idiopathic nodes in white people classified according to sex and age by decade. The number of persons examined in each group is indicated. As will be seen, the incidence of idiopathic nodes is low until the age of 60, after which it rises rapidly to nearly 30% in the ninth decade.

The present study concerns 68 families of white people with Heberden's nodes—66 of whom are women and 2 are men. A complete family history was obtained from each informant or index case, including names, ages and condition of the fingers of parents, brothers and sisters. Brothers and sisters dead before the age of 20 have been eliminated from all the following tabulations. An attempt was made to examine as many female relatives as possible. A control series of patients in City Hospital was studied for comparison. Index cases for this were women selected only if they had no arthritis of any kind and if they had sisters available for examination. Information concerning 442 individuals is included in the study series and 195 in the control series.

Of 67 mothers of affected women, 21 were said to have Heberden's nodes. These figures are based almost entirely upon history, as only 4 of these mothers were available for examination. Women with Heberden's nodes are conscious of their deformity, are disturbed at the appearance of their fingers and become observant of the condition in other people, particularly in relatives. The history of the occurrence of Heberden's nodes in this series is probably reliable. The history of absence of nodes is not so reliable, because many of the affected individuals had not seen their mothers for years prior to death and therefore had no definite knowledge concerning the condition of their mother's fingers. It seems likely that the number of affected mothers as given, if it be in error at all, is low rather than high.



Age	20-29	30-39	40-49	50-59	60-69	70-79	80-
Male	324	306	446	439	353	203	44
Female	500	498	512	306	207	125	34

FIG. 1.—*Percentage incidence of idiopathic Heberden's nodes in white people according to age.* Solid line, males; broken line, females. Figures at bottom indicate number of individuals examined in each group to determine incidence.

Of 129 sisters of affected women, 33 were said to have Heberden's nodes. Of the 33 affected women the diagnosis was confirmed by examination in 17 instances, and by response to questionnaires in 5 instances. The diagnosis was confirmed in 66% of the cases. Of 96 unaffected sisters, 20 were examined personally and 7 responded to questionnaires. The absence of Heberden's nodes was confirmed in only 28% of the cases. It seems likely that the number of affected sisters of affected women, if it be in error at all, is low rather than high.

In the control series, of 43 mothers of unaffected women, none were reported to have had lumps, knobs or enlargement of the finger joints. This is of little importance except to indicate that women without finger enlargement are not observant of the condi-

tion. Of 109 sisters of unaffected women, 5 were found to have Heberden's nodes. Four were examined and 1, a deceased sister, was accepted on the basis of history. Of the 104 unaffected sisters, 77 (74%) were examined personally. Eighteen were dead and 9 were not contacted. Of the 27 cases not contacted, 18 were below the age 50 when Heberden's nodes are rare. Any error in the series of sisters of unaffected women seems likely to be small.

TABLE 1.—OCCURRENCE OF HEBERDEN'S NODES IN RELATIVES OF AFFECTED PERSONS—68 FAMILIES.

Age groups.	Age incidence.	In 67 mothers.			In 129 sisters.		
		Total mothers.	Expected affected.	Recorded affected.	Total sisters.	Expected affected.	Recorded affected.
20–29	0.000	2	0.000	0	6	0.000	0
30–39	0.004	4	0.016	0	16	0.064	1
40–49	0.010	3	0.030	0	17	0.170	3
50–59	0.026	9	0.234	0	39	1.014	10
60–69	0.155	19	2.945	8	31	4.805	14
70–79	0.247	16	3.952	9	11	2.717	2
80–	0.294	14	3.823	4	9	2.646	3
Total	..	67	11.000	21	129	11.416	33

A further analysis of the mothers and of the sisters of affected women, comparing the number of affected persons actually found with the normal expectancy in a group of the same size and age distribution of the population in general is shown in Table 1. These figures are derived by multiplying the total number of subjects in each decade by the incidence for this age and totalling them. The number of sisters recorded affected in these families is lower than actual because the index cases have been omitted. The necessity for this procedure becomes obvious if we postulate a series of families with but 1 daughter. In such a series the occurrence would be by definition 100%. Among the 67 mothers 21 cases are reported, but only 11 cases are to be expected. This figure of expected affected is slightly high because the age of mothers as given in all but 4 cases is really the age of death. The incidence of the population in general is based on living persons, before they died. Despite this, mothers of affected women have Heberden's nodes nearly twice as frequently as the population in general. Among 129 sisters of affected women 33 cases are found, compared to 11.4 expected, about three times the normal. Among 109 sisters of unaffected women 5 cases are found, compared to 6.26 expected, a reasonably close approximation to normal. More detailed information concerning mothers and sisters of unaffected women is shown in Table 2.

Analysis of fathers and brothers of affected women will not be given in detail. Of 54 fathers concerning whom information is

available, only 1 was reported affected, compared to 4.57 expected. Of 124 brothers described, only 1 was said to be affected, compared to 4.99 expected. Of the 124 brothers, only 81 were alive and only 42 were living in Ohio. Considering only the 42 reported to be in Ohio but 1.91 was to be expected affected. It seems likely that a more thorough investigation of the available brothers will reveal a few unsuspected cases. Such search seems unlikely to alter our conclusions, so it has not yet been attempted.

TABLE 2.—OCCURRENCE OF HEBERDEN'S NODES IN RELATIVES OF UNAFFECTED PERSONS—43 FAMILIES.

Age groups.	Age incidence.	In 43 mothers.			In 109 sisters.		
		Total mothers.	Expected affected.	Recorded affected.	Total sisters.	Expected affected.	Recorded affected.
20–29 . . .	0.000	0	0.000	0	8	0.000	0
30–39 . . .	0.004	1	0.004	0	17	0.068	0
40–49 . . .	0.010	2	0.020	0	27	0.270	0
50–59 . . .	0.026	9	0.234	0	28	0.728	0
60–69 . . .	0.155	12	1.860	0	17	2.635	2
70–79 . . .	0.247	12	2.964	0	12	2.564	3
80– . . .	0.294	7	1.988	0	0	0.000	0
Total . . .	..	43	7.070	0	109	6.265	5

Various family combinations are worthy of note. Of 68 families, mothers were affected 21 times. Three generations in direct descent through the female line were found affected in 4 families. In 2 other instances grandmothers of index cases were affected, the mothers being spared. In these families, however, the mother died before the age of 35 years. Several examples of descent through the paternal line were noted. The father himself was affected only once, but in this family the mother was affected also. In 3 families a paternal aunt was affected, the father being spared. In 19 families more than 1 sister was afflicted. In only 28 of the 68 families studied was no evidence of familial involvement discovered. In 9 of these 28 families the index case was an only daughter.

In 3 families the probability of multiple involvement among brothers and sisters was calculated. This calculation can be illustrated very simply by a penny-tossing experiment. If one penny is tossed, the chance of its landing head up is 1 in 2. If a second penny is tossed, the chance of its landing head up is also 1 in 2. If both pennies are tossed together, the chance of both resting head up is 1 in 4, the product of the individual chances. The probability of a person having Heberden's nodes is the incidence. The probability of several cases occurring in the same family by chance alone is the product of their combined incidences. The first family is

illustrated by Figure 2. Four sisters are involved, 3 of whom were seen. These women were advanced in years so that the incidence is high. The probability of 4 cases occurring at this age in 1 family

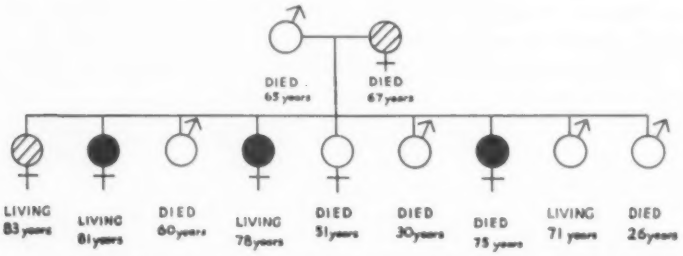


FIG. 2.—*First Family.* Black circles indicate affected individuals examined. Hatched circles affected individuals not seen. The probability for involvement of individual affected members in this family is 29.4%, 29.4%, 24.7%, 24.7%. The probability for such involvement in one family by chance alone, $0.294 \times 0.294 \times 0.247 \times 0.247 = 0.00525$. This combination might be expected to occur by chance alone once in 190 families.

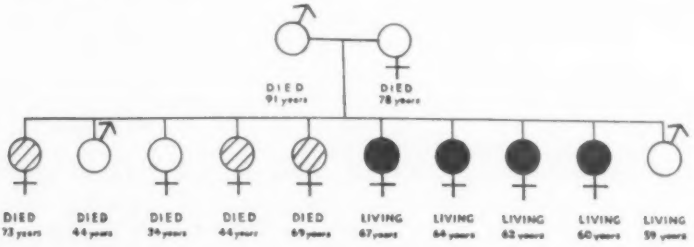


FIG. 3.—*Second Family.* The probability for individual involvement in this family is 24.7%, 1%, 15.5%, 15.5%, 15.5%, 15.5%, 15.5%. This combination can be expected to occur once in 4,500,000 families.

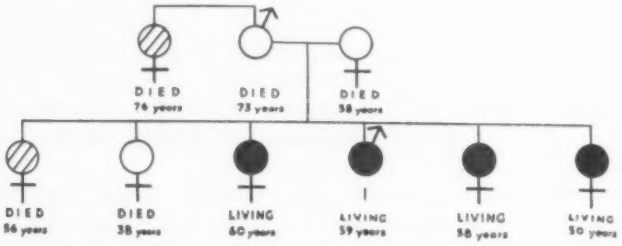


FIG. 4.—*Third Family.* The probability for individual involvement in this family is 2.6%, 15.5%, 3.6%, 2.6% and 2.6%. This combination can be expected to occur once in about 10,000,000 families.

by chance alone is 1 in 190 families. This does not seem remarkable unless we realize that this should occur once out of 190 families with at least 4 sisters who have survived until the ages of 75 to 83 years. In the second family (Fig. 3) with 7 of 8 sisters affected

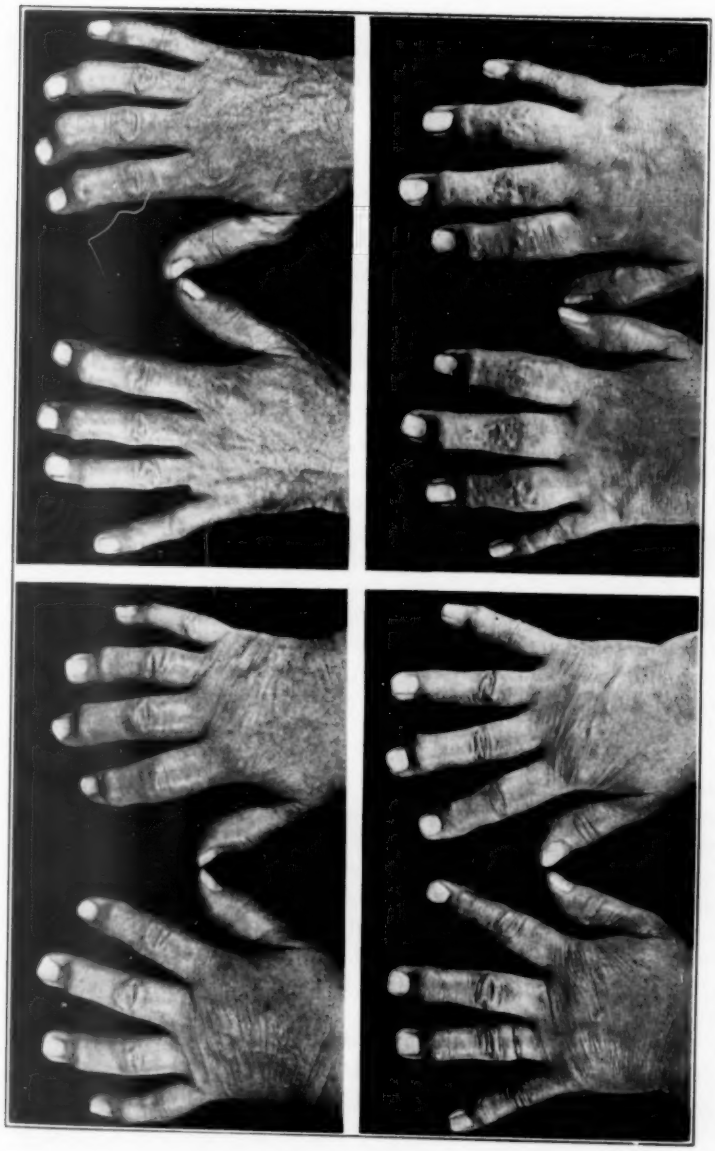


FIG. 5.—The hands of the four living affected members of the third family, showing well marked Heberden's nodes.

the probability of this combination occurring by chance alone is 1 in 4,500,000 families. Here again only 1 sister was below 50 in age. Four were in their sixties and 1 in the seventies. In the third family (Fig. 4) 4 sisters and a brother were involved. All but 1 were under 60. Here the probability is 1 in 10,000,000 families. Figure 5 shows photographs of the hands of these people. Whether we take these figures literally or not, the conclusion is unescapable that such combinations of Heberden's nodes occurring in 1 family by chance alone should be extremely rare.

Comment. This study clearly indicates the familial nature of idiopathic Heberden's nodes which is best explained by hereditary factors. The influence of common environment is eliminated because the condition occurs only in middle or later life, years after women have left the parental roof to establish their own homes and after sisters have long ceased to live together. It seems most unlikely that a common environment for the first 20 years of life might produce effects which do not become apparent for 20, 30 or 40 more years. Some type of inheritance among women is apparent but this influence in men is not so clear. The condition is relatively rare in men but it does occur. Simple dominance alone is suggested in women by the direct descent through the female line for two or three generations.

The material at hand must be analyzed by a geneticist before the exact mechanism of inheritance can be revealed. The study so far has been limited to assembling observations pertinent to the question of familial incidence. The investigation has been facilitated by certain characteristics of the disease. The deformity is so typical that the layman's opinion about its presence is reasonably reliable. The disease once present leaves a permanent record of its occurrence, and the diagnosis can be made by inspection without recourse to extensive examination or complicated technical procedures. Therefore, it was practical to determine with accuracy the incidence in the population in general. Other characteristics, however, complicate the study. The age of onset is high and many subjects free of the disease die in middle life, leaving us uncertain as to their susceptibility. Since it is a disease of later life, parents, uncles and aunts are most often not available for examination and many children are not old enough to have developed Heberden's nodes.

It may not be accurate to ascribe directly to other forms of hypertrophic arthritis all of the incidence characteristics of Heberden's nodes so far described. Definite information concerning the incidence characteristics of other forms of arthritis, showing similarities or differences between those of other arthritis and Heberden's nodes, must be observed to make these characteristics applicable. It is hoped that such similarities or differences may be apparent and

valuable conclusions drawn by analogies without the necessity of undertaking such extensive and laborious investigations as have seemed desirable in this and the previous study.

The demonstration of the influences of race, sex, age and of hereditary factors does not conclude the study of etiology in Heberden's nodes. It seems reasonable to suppose that other agencies are influential. These may operate by accelerating or retarding those organic changes necessary for the production of Heberden's nodes and thus materially affect the age of onset, or they may protect the fingers completely against the disease. The latter effect has already been observed to result from impairment of nerve function and is being studied for a report. Such other agencies influencing the onset and course of the disease, be they environmental, nutritional, circulatory, thermal, endocrinal or toxic, are not now recognizable. There is every reason to believe that, with sufficient attention, they may become so.

Conclusions. 1. Heberden's nodes or hypertrophic arthritis of the finger joints may be regarded as a distinct clinical entity. Two types are recognized and distinguishable, one arising as a result of trauma, the other arising spontaneously or idiopathically.

2. The occurrence of this disease has been shown to be profoundly influenced by race, sex, and age differences. A previous study has revealed accurately the incidences of these various classifications.

3. A study of 68 families of patients with idiopathic Heberden's nodes shows that the mothers of such subjects are affected twice as frequently and the sisters three times as frequently as the population in general. These figures, if in error at all, are more likely to be low rather than high. A control series of 43 families selected and studied in the same way showed the sisters of unaffected women to have Heberden's nodes as frequently as the population in general.

4. The occurrence of multiple cases in the same family cannot be accounted for on the basis of chance alone.

5. Hereditary factors seem best to explain the recorded observations, although the exact mechanism of transmission has not been determined.

6. The conclusions concerning Heberden's nodes are not directly applicable to other forms of hypertrophic arthritis at the present time.

REFERENCES.

(1.) **Charcot, J. M.**: Clinical Lectures on Senile and Chronic Diseases, London, The New Sydenham Society, p. 197, 1881. (2.) **Duckworth, D.**: A Treatise on Gout, London, Charles Griffin & Co., p. 71, 1889. (3.) **Monroe, R. T.**: Chronic Arthritis, New York Oxford University Press, p. 61, 1939. (4.) **Stecher, R. M.**: New England J. Med., **222**, 300, 1940. (5.) **Wick, L.**: Mitt. d. Gesellsch. f. inn. Med. u. Kinderh., **7–9**, 4, 1908.

SEASONAL VARIATION IN THE WATER CONTENT OF THE RESPIRATORY TRACT OF BIRDS AND MAMMALS.

By Eldon M. Boyd, M.A., M.D.,
PROFESSOR OF PHARMACOLOGY, QUEEN'S UNIVERSITY,
AND
G. M. Johnston, M.A.,
RESEARCH ASSISTANT IN PHARMACOLOGY, QUEEN'S UNIVERSITY,
KINGSTON, CANADA.

We have reported[1] that in albino rats the water content of the tissues of the respiratory tract varies with season. During a cold spell of weather in early autumn, an increase in water was noted and during January, February and March the tissues of the respiratory tract became considerably more dry. These seasonal variations were most pronounced in the trachea but also affected slices of lung consisting chiefly of alveolar tissue ("distal" slices) or containing a large percentage of bronchial tissue ("proximal" slices) A statistical treatment of the data indicated that the differences reported were significant ones. Seasonal variations in the water content were suggested as indicative of seasonal variations in the physiology of the respiratory tract. The albino rats used in these studies were housed in a building which in the winter months was artificially heated but not air-conditioned and it was suggested that the results might have an etiologic significance in connection with seasonal variations in respiratory tract infection in man.

To this latter suggestion might be raised the objection that the seasonal changes which were reported were those of one species only and might represent a peculiarity of that species. We have therefore extended this study to include a species from another class of the vertebrate subphylum, the common pigeon. We purposely selected a bird because we reasoned that if the same seasonal variation were encountered in a bird as in the albino rat, we would be more justified in concluding that a similar seasonal variation might also occur in man. In other words, there is less biologic difference between the albino rat and man than between the albino rat and the pigeon; if a seasonal variation in the water content of the respiratory tract were found common to albino rats and pigeons, it would seem likely that it would also be common to man.

One hundred and seventy common pigeons, *Columba livia*, were used in this seasonal study which extended from June, 1939, to September, 1940. A similar number of albino rats were run at the same time to confirm the results of the previous winter.[1] To substantiate the results in the pigeons, tests were made from time to time on a total of some 90 white leghorn cockerels.

Pigeons. At approximately monthly intervals, 10 pigeons were killed without anesthesia by quickly wringing their necks. The

body cavity was opened, the trachea freed as high up as possible and the lungs quickly dissected away from the dorsal wall. As in our previous work on albino rats,[1] the removed parts were divided into three sections: first, the trachea; second, slices of the distal half of each lung taken centrifugally from the hilus; and third, the proximal half of each lung next the hilus. This division of the lung parenchyma had been made in rats because one section contained chiefly alveolar tissue while the other contained a good deal of bronchial tissue. For purposes of uniformity the same sections were made in pigeons. In pigeons, however, one section did not contain chiefly alveolar tissue and the other a preponderance of bronchial tissue as in the rat because the lung of a pigeon differs anatomically from that of the rat. In birds, air passes directly to air sacs at the periphery of the lung through the two mesobronchi and their branches the entobronchi, and respiratory exchange occurs chiefly during expiration as air is forced back from the periphery through the parabronchi and parabronchial air capillaries into the mesobronchi again and thence out through the trachea.[2] We have noted a uniformity of appearance, consistency and water content in all parts of the lung of pigeons, in contrast to the rat where significantly different sections may be isolated,[1] and the diagram presented by Graham[2] indicates that bronchial and alveolar tissues are distributed approximately evenly throughout the pigeon lung. The only advantage we gained in dividing the pigeon lung into distal and proximal sections was therefore the obtaining of duplicate water estimates on lung parenchyma, duplicates which agreed remarkably well as may be seen in Chart 1.

As the three sections were removed from each pigeon, they were separately placed in cleaned, dried and weighed weighing bottles and the wet weight estimated to the nearest 0.1 mg. Ground glass stoppers were then lightly inserted and the sections were dried at 90° C. for 100 hours in a drying oven. After cooling, they were reweighed and from the differences in weight the water content was calculated in gm. per 100 gm. of original tissue (per cent water). All of the dissection and weighing manipulations were done as quickly as possible to minimize loss of water. Since the room in which these operations were carried out was dry-heated in the winter months and the relative humidity greatly reduced, we considered the possibility that more water might be evaporated from lung sections removed during the winter months and before we could determine their wet weight. To investigate this possibility, we compared the average wet weights of sections from 10 birds removed in the ordinary dry winter air with the average of sections from 10 other birds removed in the same room with the relative humidity artificially raised to the summer level by water evaporated from shallow pans. We found the average water contents practically identical under the two circumstances which indicated that our

technique was sufficiently rapid that neglible amounts of water were evaporated during dissection and before wet weights were determined.

When the water content of the respiratory system of pigeons was measured at different seasons of the year, we obtained the results shown in Chart 1. Each point on these plottings represents the

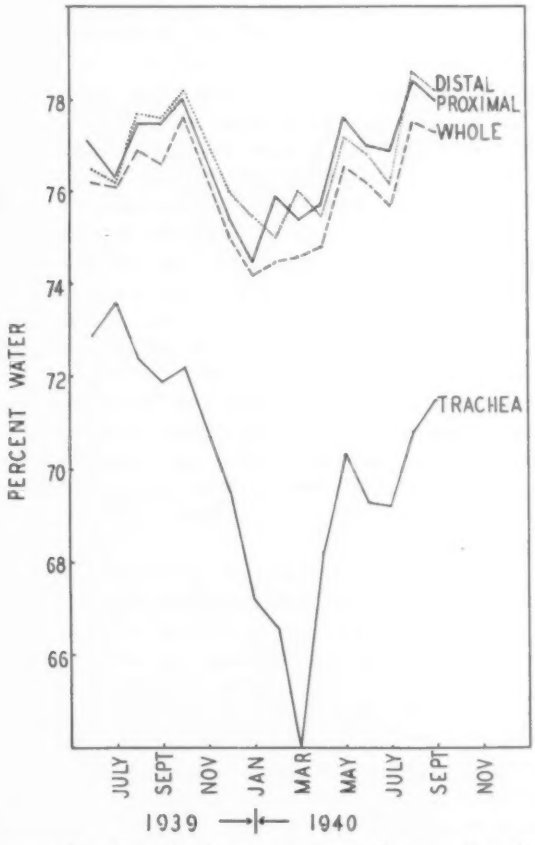


CHART 1.—Seasonal variation in the water content of the trachea, distal half and proximal half of the lungs and in the whole respiratory tract of pigeons.

mean of 10 pigeons and separate curves have been drawn for the trachea, the distal half of each lung, the proximal half of the lungs and finally the whole respiratory tract. It may be seen that there occurred a distinct fall in the water content of all sections in the winter months. The respiratory system was distinctly more dry during January, February and March. This corresponds with the results previously obtained in rats.[1] We did not notice any sharp,

distinct rise in water content in the early autumn of 1939 as we had seen in rats in October of 1938, although the mean values for lung water of pigeons were slightly higher at this season in 1939. Evidently the early autumn rise in water content does not occur as consistently as the midwinter fall. These results in pigeons therefore substantiated our previous findings in the albino rat.

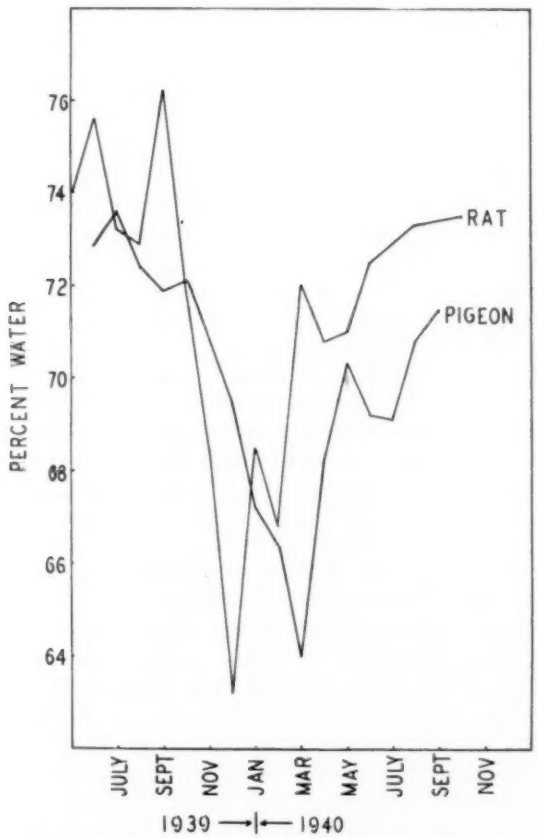


CHART 2.—A comparison of seasonal variations in the water content of the trachea of albino rats and pigeons.

Albino Rats. It was considered advisable to repeat our seasonal study on the water content of the respiratory system of albino rats, first in order to confirm our results of the season 1938–1939 and secondly to see if there was any variation from year to year. One hundred and fifty young albino rats weighing 150 to 200 gm. were used. The results in general were similar in the season 1939–1940 to the season 1938–1939. The early autumn rise in lung water was

not nearly as marked in 1939 as in 1938. The curves obtained in the albino rats during 1939–1940 were, in fact, almost identical to those obtained in the pigeon during the same year and to illustrate this similarity we have plotted the seasonal changes in tracheal water of the two species and compared these in Chart 2.

The most marked and consistent seasonal change over 2 years in one species and over 1 year in two species was the midwinter drying of the respiratory system, especially the trachea which lost up to 15% of its water in midwinter. This occurred in two biologically distinctly different species belonging to two different classes of the vertebrate subphylum. Factors common to the two species were that the results were obtained in the same locality—southeastern Ontario—and both species were housed in a building which was dry-heated in the winter months. We have as yet no experimental data to indicate whether either or both of these common factors are significant. Our present results, however, substantiate our previous[1] suggestion that similar midwinter drying of the respiratory system may occur in man and be related to respiratory infection at this time. Proof of this suggestion can be obtained only by actual measurements in man.

Cockerels. Our results of a similar seasonal study of some 90 cockerels were less consistent due, we believe, to the fact that we were unable to obtain cockerels of the same size throughout the year. We had contracted with a local poultry farm for one-pound white leghorn cockerels to be supplied each month throughout the year. We then housed these birds in our animal quarters for 1 month before killing them. Breeding and hatching had not been attempted before on this particular poultry farm in the winter months and it was found impossible to breed and hatch satisfactory chicks in the winter. We were forced to use adult hens in the winter and found that their respiratory tract was drier than that of the young cockerels. A similar drying effect of age was noted in albino rats.[1] In the following summer we compared the water content of the respiratory tract of hens with that of cockerels on the same day and used the difference as a factor to correct for the use of older birds in the winter. When this correction was made, the results were rather erratic, as might be expected, but in practically all instances the water content of the respiratory tract was lower in the winter months than during the rest of the year. We have therefore established that in three species—rats, pigeons and cockerels—there occurs a drying of the respiratory tract during the midwinter months of January, February and March, and occasionally into April.

Conclusions. We have confirmed our previous[1] observation that a distinct drying of the lungs and trachea occurs in albino rats during January, February and March in a dry-heated building in this locality (southeastern Ontario). A similar midwinter drying

of the respiratory system was further found to occur in two species of another class of the vertebrates, namely pigeons and cockerels. It seems reasonable to suggest that a similar drying may occur in man and have an etiologic significance in connection with seasonal variation in susceptibility to infection of the respiratory system.

The authors wish to thank Mr. E. R. Angehrn and the Ciba Company, Ltd., of Montreal for a grant which defrayed part of the expenses of this investigation.

REFERENCES.

(1.) **Boyd, E. M.,** and **Johnston, G. M.**: Am. J. Med. Sci., **199**, 246, 1940. (2.) **Graham, J. D. P.**: J. Physiol., **97**, 133, 1939.

THE EFFECT OF PHENOBARBITAL ON NORMAL AND IMPAIRED DEXTROSE TOLERANCE.

By J. A. Rosenkrantz, M.D.,
HOUSE PHYSICIAN IN MEDICINE,

AND

Maurice Bruger, M.D.,
ASSISTANT CLINICAL PROFESSOR OF MEDICINE, AND CHIEF, DIVISION OF PATHOLOGICAL CHEMISTRY, NEW YORK CITY.

(From the Department of Medicine, New York Post-Graduate Medical School and Hospital, Columbia University.)

Many investigators have studied the effect of barbiturates on carbohydrate metabolism of animals. Britton[4] and Mulinos[14] anesthetized cats with amytal and observed little or no change in the blood sugar for several hours after its administration. Page[16a,b] working with dogs and rabbits and Cori[5] with rats showed that amytal was without effect on carbohydrate metabolism. Atnan and Fenz[1] demonstrated no change in the blood sugar of patients with diabetes mellitus after the administration of evipal intravenously. More recently, Hrubetz and Blackberg[12a,b] and Hrubetz, Blackberg and Dotti[13] showed that barbiturates produced no alterations in the blood sugar of starved or normally fed rabbits during deep anesthesia; a decrease in blood sugar was noted during the recovery phase. Zerfas and McCallum[21] and Dresbach and Randles[7] observed no change in the blood sugar of normal fasting animals given anesthetic doses of barbiturates.

Underhill and Sprunt[18] and Hines, Boyd and Leese[10a,b] demonstrated an increase in blood sugar of rabbits and dogs anesthetized with amytal. Weiss,[19] investigating the effect of soluble barbital and phenobarbital on carbohydrate metabolism in dogs and cats, found a sudden rise in blood sugar which reached a maximum in 1 to 2 hours and returned to normal within 6 to 20 hours. Bang[2] reported hyperglycemia in rabbits given barbital. Wierzuchowski and Gadomska[20] observed an increased blood sugar in dogs after

the administration of amytal. Hines, Leese and Barer[11] showed that dogs cannot store glycogen and have a decreased ability to assimilate dextrose after the administration of amytal. Olmsted and Giragossintz[15a,b] studied dextrose tolerance in dogs given barbital and concluded that there was no obvious change in carbohydrate metabolism when the animals were given a meat diet exclusively. When the dogs were fed a diet containing meat and carbohydrate, a definite hyperglycemia resulted.

Ellis and Barlow[8] noted a decrease in the blood sugar of cats and pigeons during the first 24 hours of barbital anesthesia.

Obviously, no definite conclusion can be drawn concerning the effect of barbiturates on carbohydrate metabolism. Whether the variability of results may be attributed to the different types of barbiturates used or to the lack of uniformity in the use of animal species is problematic.

Since dextrose tolerance tests are commonly performed as an aid in the diagnosis of various endocrine disorders, particularly diabetes mellitus, it seemed important to know whether barbiturates, when used in physiologic doses, would modify the normal or impaired dextrose tolerance curve. In the present study, human subjects were used and the barbiturate employed limited to phenobarbital.

Material and Methods. Thirty-seven subjects were selected from the clinics of the New York Post-Graduate Hospital. Eighteen had minor or negligible ailments and exhibited normal tolerance for sugar; 19 were either frank diabetics or prediabetics as indicated by a failure of the blood sugar to return to 120 mg. per 100 cc. or less after the ingestion of a standard amount of dextrose. All subjects were ambulatory and the diet was kept as constant as possible during the period of study. Insulin was not used by the diabetics at any time, since the glycosuria was fairly well controlled by a restricted carbohydrate intake. Sedatives had not been used prior to the test for at least several weeks, if at all. The subjects appeared in the early morning without breakfast and no smoking[6] was permitted. Urine and venous blood specimens were obtained. Each person was then given 100 gm. of dextrose in a 50% aqueous solution by mouth. Blood and urine samples were collected at 30, 60 and 120 minutes after the ingestion of the dextrose. The chemical determinations were begun within 10 minutes after collection. Blood sugars were determined by the Folin-Wu method,[9] urines qualitatively by a modified Nylander reagent (Galatest) and quantitatively, where indicated, by the Benedict method.[3]

Each of 24 subjects (13 with normal dextrose tolerance and 11 with impaired tolerance) ingested 0.066 gm. of phenobarbital 3 times a day for 7 days and on the morning of the eighth day, the dextrose tolerance was again determined under identical conditions. It is fair to assume that the phenobarbital was taken as ordered since each complained of the marked sedative effect of the drug; moreover, this was further evident objectively. It was planned to have these subjects return a third time for similar tests after discontinuing phenobarbital for 7 days, but since many objected to the frequent venipunctures, this plan was discarded. As a control series, therefore, 13 subjects (5 with normal dextrose tolerance and 8 with impaired tolerance) were given placebos (calcium carbonate, 0.3 gm., 3 times daily for 7 days) and dextrose tolerance tests carried out before and after the ingestion of the calcium carbonate.

Results. In order to conserve space, the individual blood sugar curves are not recorded. The observation appeared to be fairly consistent throughout the study, namely, that normal subjects or patients with diabetes or prediabetes frequently showed an increased tolerance for dextrose on reëxamination 1 week after an initial study.

Chart 1 demonstrates that the increased tolerance for carbohydrates in normal subjects after ingesting phenobarbital is apparent and not real. The similarity in the mean curves for both the phenobarbital and placebo groups is striking. Chart 2 shows that

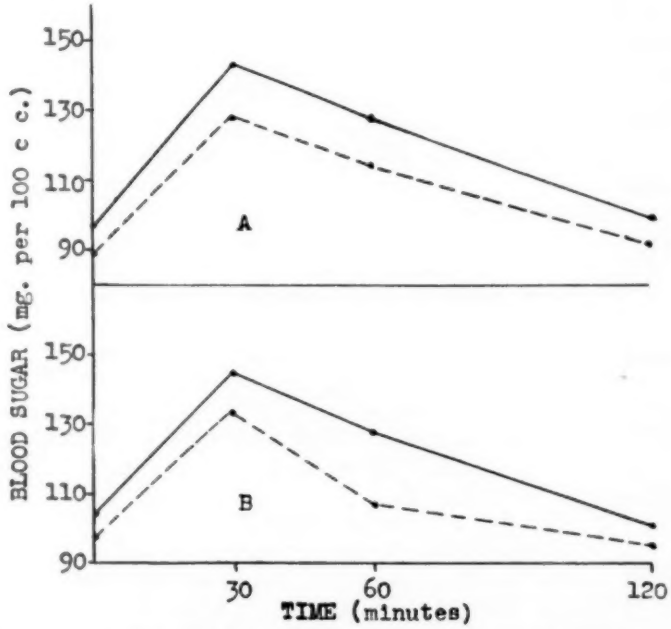


CHART 1.—*A*, The solid line indicates the mean dextrose tolerance curve in 13 normal subjects prior to the ingestion of phenobarbital, and the broken line the mean dextrose tolerance curve after the ingestion of 0.2 gm. of phenobarbital daily for 7 days. *B*, The solid line indicates the mean dextrose tolerance curve in 5 normal subjects prior to the ingestion of placebos, and the broken line the mean dextrose tolerance curve after the ingestion of 1 gm. of calcium carbonate daily for 7 days.

the impaired dextrose tolerance of patients with diabetes or prediabetes is modified to a greater extent by the ingestion of phenobarbital than it is by placebos. Although the dextrose tolerance is increased in both groups, the increase in tolerance is definitely greater in those patients receiving phenobarbital.

Discussion. One obvious reason to explain the increased tolerance for carbohydrate manifested by most persons reappearing for a repeat dextrose tolerance test may be ascribed to the fact that most of the anxiety and nervousness exhibited by the subject during

the initial study is subsequently distinctly lessened. This is probably due to the fact that on reëxamination the individual is now acquainted with the routine and environment. Recently, Robinson

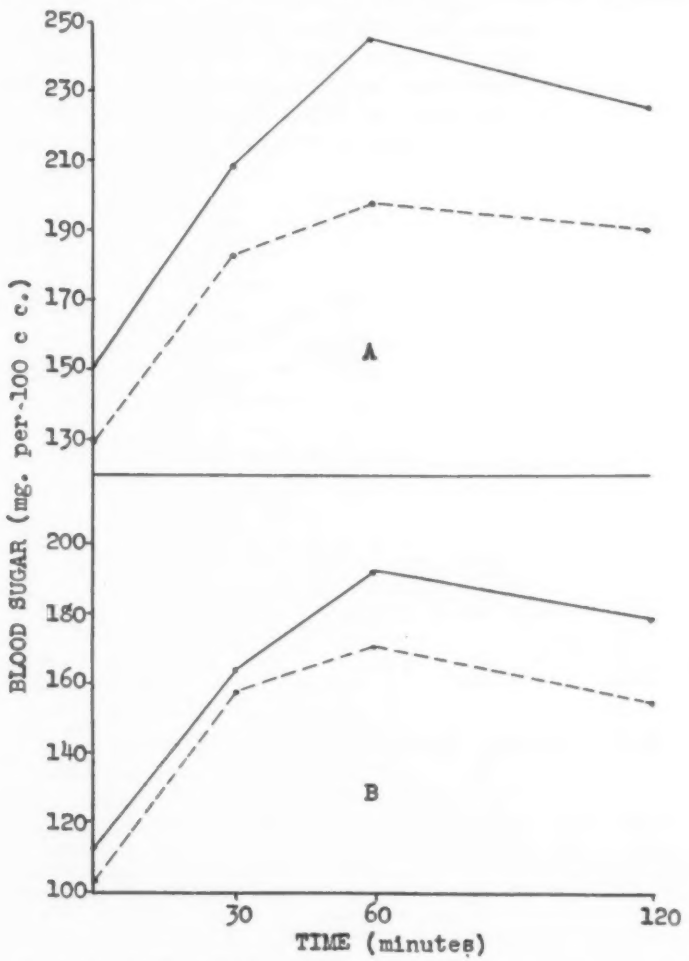


CHART 2.—*A*, The solid line indicates the mean dextrose tolerance curve in 11 subjects with impaired sugar tolerance prior to the ingestion of phenobarbital, and the broken line the mean dextrose tolerance curve after the ingestion of 0.2 gm. of phenobarbital daily for 7 days. *B*, The solid line indicates the mean dextrose tolerance curve in 8 subjects with impaired sugar tolerance prior to the ingestion of placebos, and the broken line the mean dextrose tolerance curve after the ingestion of 1 gm. of calcium carbonate daily for 7 days.

and Shelton[17] have shown that overanxious types of individuals may show sufficient disturbance in the utilization of carbohydrate to impair definitely the dextrose tolerance curve.

Phenobarbital, however, appears to exert a specific effect on the impaired dextrose tolerance of diabetics and prediabetics. One can only speculate on the actual mechanism involved. Hrubetz and Blackberg[12b] have shown that although phenobarbital is not excreted by the liver, it nevertheless depresses the glycogenolytic power of that organ as indicated by the response of the blood sugar to epinephrine. It is conceivable that this inhibition of liver glycogenolysis may account for the increased tolerance observed in patients with diabetes and prediabetes after the ingestion of phenobarbital.

Conclusions. 1. All factors which tend to modify the dextrose tolerance curve being kept as constant as possible, normal subjects or patients with diabetes or prediabetes frequently show an increased tolerance for dextrose on reëxamination 1 week after an initial study. This increase in tolerance for sugar may be ascribed to the fact that most persons reappearing for the subsequent study show a diminution in anxiety and nervousness.

2. The increase in dextrose tolerance in subjects with normal sugar tolerance receiving phenobarbital is apparent and not real; normal subjects receiving placebos show approximately the same increase in dextrose tolerance. Phenobarbital is shown, therefore, to exert no specific effect on normal dextrose tolerance.

3. The increase in dextrose tolerance in patients with impaired sugar tolerance receiving phenobarbital is greater than in those receiving placebos. Phenobarbital, therefore, affects specifically the impaired dextrose tolerance curve probably by virtue of its ability to inhibit glycogenolysis in the liver.

REFERENCES.

(1.) **Atnan, A.**, and **Fenz, E.**: Wien. Arch. f. inn. Med., **30**, 301, 1937. (2.) **Bang, I.**: Biochem. Ztschr., **58**, 236, 1913. (3.) **Benedict, S. R.**: J. Am. Med. Assn., **57**, 1193, 1911. (4.) **Britton, S. W.**: Am. J. Physiol., **74**, 291, 1925. (5.) **Cori, C. F.**: Proc. Soc. Exp. Biol. and Med., **23**, 127, 1925. (6.) **Dill, D. B., Edwards, H. T.**, and **Forbes, W. H.**: Am. J. Physiol., **109**, 118, 1934. (7.) **Dresbach, M.**, and **Randles, F. S.**: J. Pharm. and Exp. Ther., **42**, 273, 1931. (8.) **Ellis, M. M.**, and **Barlow, O. W.**: Ibid., **24**, 259, 1924. (9.) **Folin, O.**, and **Wu, H.**: J. Biol. Chem., **41**, 367, 1920. (10.) **Hines, H. M., Boyd, J. D.**, and **Leese, C. E.**: (*a*) Proc. Soc. Exp. Biol. and Med., **23**, 228, 1925; (*b*) Am. J. Physiol., **76**, 293, 1926. (11.) **Hines, H. M., Leese, C. E.**, and **Barer, A. P.**: Proc. Soc. Exp. Biol. and Med., **25**, 736, 1928. (12.) **Hrubetz, M. C.**, and **Blackberg, S. N.**: (*a*) Ibid., **34**, 65, 1936; (*b*) Am. J. Physiol., **122**, 759, 1938. (13.) **Hrubetz, M. C., Blackberg, S. N.**, and **Dotti, L. B.**: Proc. Soc. Exp. Biol. and Med., **35**, 303, 1936. (14.) **Mulinos, M. G.**: J. Pharm. and Exp. Ther., **34**, 425, 1928. (15.) **Olmsted, J. M. D.**, and **Giragossintz, G.**: (*a*) Proc. Soc. Exp. Biol. and Med., **27**, 103, 1929; (*b*) J. Lab. and Clin. Med., **16**, 354, 1931. (16.) **Page, I. H.**: (*a*) Ibid., **9**, 194, 1923; (*b*) Am. J. Physiol., **66**, 1, 1923. (17.) **Robinson, G. W., Jr.**, and **Shelton, P.**: J. Am. Med. Assn., **114**, 2279, 1940. (18.) **Underhill, F. P.**, and **Sprunt, D. H.**: Proc. Soc. Exp. Biol. and Med., **25**, 137, 1927. (19.) **Weiss, S.**: Ibid., **23**, 363, 1926. (20.) **Wierzuchowski, M.**, and **Gadomska, H.**: Biochem. Ztschr., **191**, 398, 1927. (21.) **Zerfas, L. G.**, and **McCallum, J. T. C.**: J. Indiana Med. Assn., **22**, 47, 1929.

DIETARY HYPERCHOLESTEROLEMIA.*

By Alfred Steiner, M.D.,
RESEARCH FELLOW, RESEARCH SERVICE, FIRST DIVISION, WELFARE HOSPITAL; INSTRUCTOR IN MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY,

AND

Beatrice Domanski, B.A.,
TECHNICIAN,
NEW YORK CITY.

(From the Research Service, First Division, Welfare Hospital, Department of Hospitals, and the Department of Medicine, College of Physicians and Surgeons, Columbia University.)

There has been much controversy as to whether or not an alteration of the serum cholesterol level can be effected by dietary means. Former studies[1,2,6–8] are at variance as to whether or not alimentary hypercholesterolemia results from the ingestion of a single fatty meal. Gardner and Gainsborough[5] reported that no elevation of the cholesterol level could be obtained by one feeding, but that moderate changes could be produced by the prolonged feeding of diets rich or poor in fats. In a previous communication[11] it was reported that the serum cholesterol was not significantly altered by diets, rich or poor in fat and cholesterol in 5 of 9 patients during two 6-week periods. The fat content of the diet during the first period was 300 gm. daily and during the second less than 50 gm. daily. In 4 of the individuals a slight rise of serum cholesterol occurred during the high fat régime.

A recent article by Corwin,[4] however, in which a marked alimentary hypercholesterolemia was produced in dogs by the feeding for 6 weeks of lecithin obtained from the adrenal gland, clearly demonstrated for the first time that the serum cholesterol could be elevated by dietary means. It was therefore considered of interest to determine: 1, if a similar alimentary hypercholesterolemia could be produced in humans; and, 2, if a prolonged alimentary hypercholesterolemia in dogs would result in arterial lesions.

1. **The Effect on the Serum Cholesterol Level of Egg Yolk Powder Feeding in Humans.** A group of 10 patients was studied. Eight had been hospitalized for rheumatoid arthritis and 2 for chronic nephritis without edema. Because pure lecithin was not available, egg yolk powder† was used as a crude source of this substance. An analysis† of the egg yolk powder showed it to contain lecithin, 14.4%; vitellin, 31.6%; nuclein, 3%; cerebrin, 0.6%; glycerophosphoric acid, 2.4%; cholesterol, 8%; fats, 40.6%; coloring matter, 1%; salts, 2%; and water, 3.6%. One hundred grams of egg

* This investigation was aided in part by a grant from the Josiah Macy, Jr., Foundation.

† R. C. Williams & Co., New York City.

yolk powder, equivalent to 31 gm. of protein and 67 gm. of fat (720 calories), in addition to the regular high caloric diet (2500 calories), was fed to the 10 patients for from 6 to 10 weeks after an initial control period of 3 to 4 weeks. A second period of egg yolk powder feeding was studied in 2 of the individuals. The egg yolk powder was fed in 50-gm. portions twice daily after being suspended in about 3 oz. of milk with sugar and vanilla added for flavoring.

Total serum cholesterol was determined weekly by the method of Bloor, Pelkan and Allen.[3]

TABLE 1.—EFFECT OF EGG YOLK POWDER FEEDING ON THE SERUM CHOLESTEROL IN 10 PATIENTS.

No.	Patient.	Age.	Sex.	Diagnosis.	Control period, average.	Egg yolk powder feeding period.							Control period.	
						Weeks.					Maximum increase.		Subsequent base line.	Weeks before returning to base line.
						2.	4.	6.	8.	10.	Mg.	%		
1	H.T.	31	M	Rheumatoid arthritis	195 ± 13	245	225	235	...	...	50	25	195	2
2	E.C.	38	F	"	284 ± 7	360	454	330	...	...	170	58	290	2
3	A.G.	37	F	"	208 ± 2	243	260	260	245	...	52	25	220	3
4	J.G.	29	M	"	230 ± 5	280	270	315	298	278	95	41	220	1
5	M.S. (a)	31	F	"	245 ± 5	284	315	280	284	...	70	29	225	2
	(b)				230 ± 5	275	315	333	...	...	103	44	230	3
6	R.B.	34	F	"	219 ± 7	249	276	300	333	280	114	47	225	3
7	J.L. (a)	27	F	"	185 ± 5	208	220	263	281	279	96	51	200	5
	(b)				235 ± 5	279	290	314	276	...	80	37	225	3
8	M.S.	23	F	"	202 ± 6	208	215	230	240	264	62	30	206	2
9	M.M.	28	F	Chronic nephritis	281 ± 31	333	350	385	325	...	104	35	275	5
10	M.P.	18	F	"	325 ± 44	417	417	543	...	...	218	67		

Cholesterol values expressed in mg. per 100 cc.

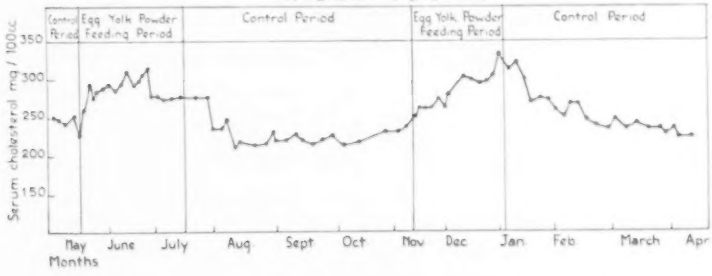
Table 1 contains the average serum cholesterol during the initial control period in the 10 patients studied. It also shows the serum cholesterol determinations after 2, 4, 6, 8, or 10 weeks of egg yolk powder feeding with the maximum increase and the maximum per cent increase. The subsequent base line attained by serum cholesterol and the number of weeks required to reach this level are also recorded. From this table it can be seen that during the initial control period, the serum cholesterol remained relatively constant in 8 of the 10 patients. The deviation from the average varied from 2 to 13 mg. This finding has been commented upon previously.[10,11] The 2 patients in whom the serum cholesterol level fluctuated widely were cases of chronic nephritis. Edema was not present in these individuals. It can also be seen from Table 1 that following the ingestion of egg yolk powder the serum cholesterol level in each patient increased, reaching a maximum in 2 to 8 weeks. The increase in serum cholesterol varied from 50 to 218 mg., the average

increase being 101 mg. The percentage increase in serum cholesterol varied from 25% to 67%, the average being 41%. After discontinuance of egg yolk powder feeding, the serum cholesterol level gradually diminished, returning to a relatively constant base line in from 1 to 5 weeks. Chart 1 illustrates the variation in the serum cholesterol level during and subsequent to 2 periods of egg yolk powder feeding in Patient 5.

Chart I

EFFECT OF EGG YOLK POWDER FEEDING ON THE SERUM CHOLESTEROL LEVEL

In Patient # V (M.S. # 31)



2. **Effect of Prolonged Egg Yolk Powder Feeding in Dogs.** In the second phase of this study 100 gm. of egg yolk powder were fed daily to 4 mongrel dogs, 3 male and 1 female. This was added to 200 gm. of regular dog food which contained 20% protein, 60% carbohydrate, and 2% fat. There were four periods of egg yolk powder feeding for each animal totalling from 44 to 56 weeks. Four control periods were interspersed between the egg yolk powder feeding periods and varied from 4 to 6 weeks each.

Serum cholesterol determinations were done weekly by the method of Bloor, Pelkan and Allen.[3] At the end of the experiment the animals were sacrificed and autopsied.

Table 2 records the serum cholesterol determinations obtained during the control and egg yolk powder feeding periods, 4 of each, in the animal experiment. From the data presented it is seen that in each of the 4 dogs the serum cholesterol increased following the ingestion of egg yolk powder. The maximum increase varied from 155 to 251 mg., with an average of 203 mg. Chart 2 illustrates the fluctuation of serum cholesterol level in Dog 3 during the control and egg yolk powder feeding periods.

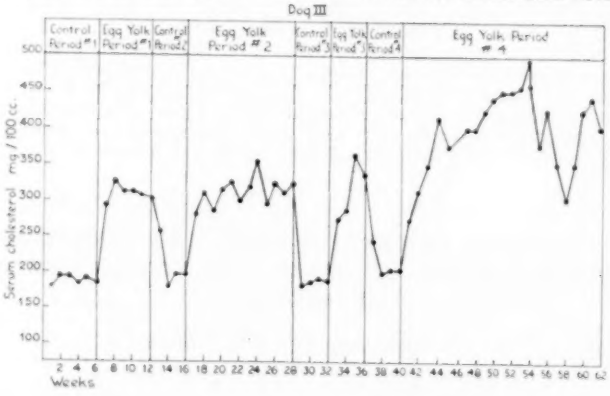
The animals were sacrificed at the end of the experiment by air embolus. Gross examination of the organs revealed no structural changes beyond wrinkling of the intima of the aorta in 2 of the 4 instances. This was confined to the arch and ascending portion of the aorta. Microscopic sections showed only one area of intimal fibrous thickening in one aorta. Anisotropic fat and cholesterol clefts were not present in this lesion. Lipoid infiltration was not present in the liver, lung, kidney or spleen.

TABLE 2.—EFFECT OF EGG YOLK POWDER FEEDING ON THE SERUM CHOLESTEROL LEVEL IN DOGS.

	Dog 1.	Dog 2.	Dog 3.	Dog 4.
Control period No. 1:				
No. of weeks	6	6	6	6
Average serum cholesterol	200 ± 7	168 ± 10	190 ± 5	333 ± 6
Egg yolk feeding period No. 1:				
No. of weeks	6	6	6	6
Highest serum cholesterol	333	278	324	417
Control period No. 2:				
No. of weeks	4	4	4	4
Base line serum cholesterol	188	151	184	312
Egg yolk feeding period No. 2:				
No. of weeks	12	12	12	12
Highest serum cholesterol	312	245	355	500
Control period No. 3:				
No. of weeks	4	4	4	4
Base line serum cholesterol	196	175	185	334
Egg yolk feeding period No. 3:				
No. of weeks	4	4	4	4
Highest serum cholesterol	282	246	384	500
Control period No. 4:				
No. of weeks	..	..	..	..
Base line serum cholesterol	211	158	200	368
Egg yolk feeding period No. 4:				
No. of weeks	34	34	22	34
Highest serum cholesterol	400	323	497	584
Total no. of weeks of egg yolk feeding	56	56	44	56
Maximum increase in serum cholesterol, all periods	200	155	207	251

Chart II

EFFECT OF EGG YOLK POWDER FEEDING ON THE SERUM CHOLESTEROL LEVEL



Comment. An alimentary hypercholesterolemia has been produced in humans and in dogs by feeding egg yolk powder for periods varying from a month to a year. The lecithin content of the egg yolk powder appears to be the important factor in the elevation of the serum cholesterol because comparable effects were not obtained by diets rich in fat and cholesterol even with the addition of 10 gm. of crystalline cholesterol daily.[11] All except 1 of the patients gained

body weight during the egg yolk powder feeding period. This finding will be described elsewhere.*

The elevations in serum cholesterol occurring in dogs as a result of egg yolk powder feeding were not as great as those obtained by Corwin[4] when feeding 50 gm. of pure lecithin daily. However, the 100 gm. of egg yolk powder contained only 14 gm. of lecithin. At postmortem examination no atheromatous lesions of the aorta or coronary arteries were found. Indeed, experimental lesions of this nature have never been produced in the dog. However, the elevations of the serum cholesterol in these animals did not compare with those high levels obtained in rabbits by cholesterol feeding,[9] and, therefore, the possibility that experimental atherosclerosis in dogs would occur in the presence of more marked hypercholesterolemia is not excluded.

Conclusions. 1. Ten patients, 8 with rheumatoid arthritis and 2 with chronic nephritis, were fed egg yolk powder containing 14% lecithin for 6 to 10 weeks. The serum cholesterol in each increased from 50 to 218 mg. with an average rise of 101 mg.

2. A hypercholesterolemia was produced in 4 dogs by the feeding of egg yolk powder for from 44 to 56 weeks. The elevation in serum cholesterol ranged from 155 to 251 mg.

3. The moderate hypercholesterolemia in 4 dogs did not result in significant arterial lesions.

REFERENCES.

(1.) **Blix, G.**: Acta med. Scandin., **64**, 142, 1926. (2.) **Bloor, W. R.**: J. Biol. Chem., **23**, 317, 1915. (3.) **Bloor, W. R., Pelkan, K. F.**, and **Allen, D. M.**: Ibid., **52**, 191, 1922. (4.) **Corwin, W. C.**: Arch. Path., **26**, 456, 1938. (5.) **Gardner, J. A.**, and **Gainsborough, H.**: Biochem. J., **22**, 1048, 1928. (6.) **Knudson, A.**: J. Biol. Chem., **45**, 225, 1921. (7.) **McClure, C. W.**, and **Huntsinger, M. E.**: Ibid., **76**, 1, 1928. (8.) **McMaster, P. D.**: J. Exp. Med., **40**, 25, 1924. (9.) **Steiner, A.**: Proc. Soc. Exp. Biol. and Med., **39**, 411, 1938. (10.) **Steiner, A.**, and **Turner, K. B.**: J. Clin. Invest., **19**, 373, 1940. (11.) **Turner, K. B.**, and **Steiner, A.**: Ibid., **18**, 45: 1939.

THE INCIDENCE OF CERTAIN SIGNS AND SYMPTOMS AT VARIOUS LEVELS OF BASAL AND TOTAL RESTING METABOLISM.

An Analysis of 1000 Cases.

By J. J. Short, M.D., F.A.C.P.,

ASSOCIATE CLINICAL PROFESSOR OF MEDICINE, NEW YORK POST-GRADUATE MEDICAL SCHOOL OF COLUMBIA UNIVERSITY, NEW YORK, N. Y.

(From the records of the Life Extension Examiners, 11 E. 44th St., New York City.)

Although it is recognized that certain signs and symptoms are generally associated with certain levels of metabolic rate, it is rather difficult to find from the literature their average incidence

* Unpublished data.

at different rate levels. Believing that a statistical analysis of this question would be of value, a study has been made of 1000 records of individuals having had carefully performed basal metabolisms.

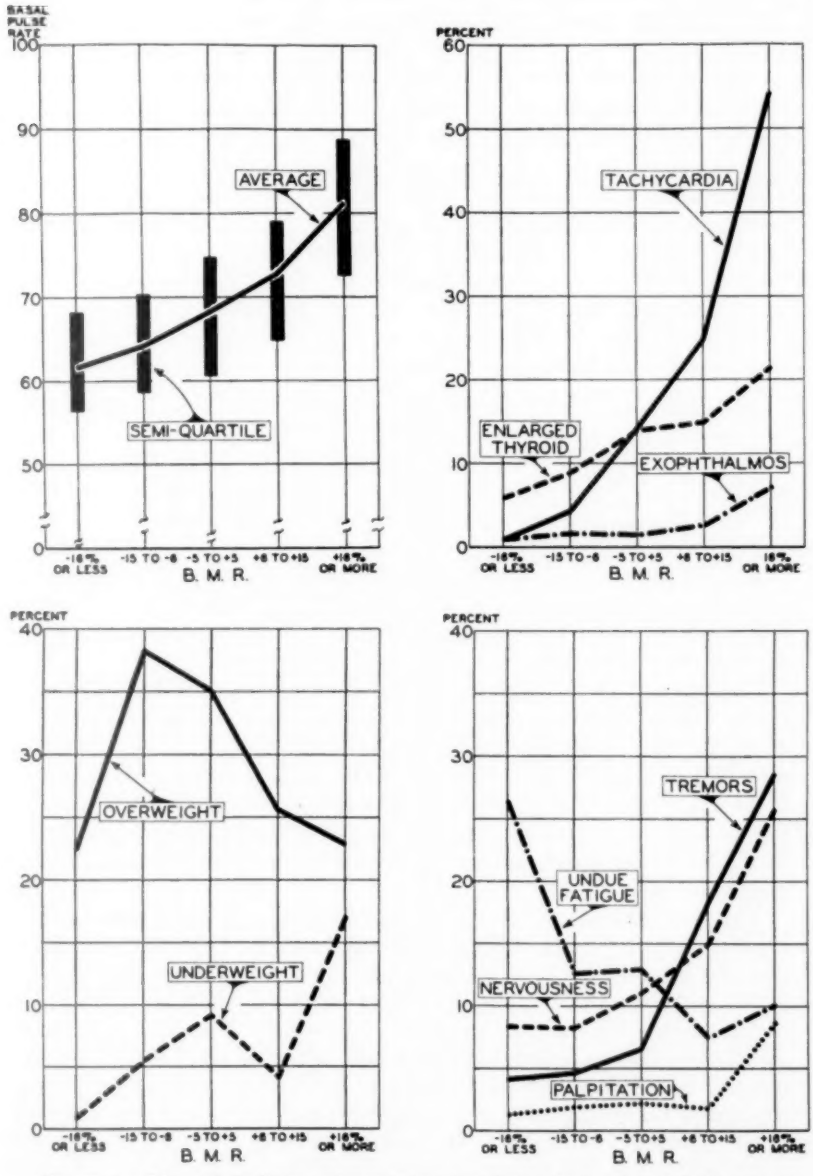


CHART 1.—Physical findings and symptoms in relation to basal metabolic rate of 1000 cases.

The metabolic rates have been given the primary consideration and such findings as pulse rate, tachycardia, enlarged thyroid, exophthalmos, overweight, underweight, tremors, undue fatigue, "nervousness" and palpitation have been correlated with the basal rate levels without regard to the diagnosis. The results are portrayed in Chart 1.

Basal metabolic rates have been grouped as follows: −16% or less, −15 to −6%, −5 to +5%, +6 to +15%, and +16% or more. The distribution of cases is shown in Table 1.

TABLE 1.—DISTRIBUTION ACCORDING TO BASAL METABOLIC RATES OF 1000 CASES.

Groups.	Males.	Females.	Total.	Average B.M.R., %.
−16% or less	54	67	121	−19 2
−15 to −6%	142	187	329	−10 0
−5 to +5%	140	219	359	− 0 9
+6 to +15%	46	75	121	+ 9 5
+16% or more	30	40	70	+27 9

Although only the semi-quartile range of basal pulse rates has been listed, one is impressed immediately with the wide variation which exists at each level of basal metabolism. Even though the average trend is regularly upward, this chart represents the futility of any attempt to estimate basal metabolism from the pulse rate alone.

For the purposes of this study tachycardia was defined as a pulse rate of 80 or above under basal conditions. It will be noted that the incidence of tachycardia increased sharply with each increased level of basal metabolic rate.

Enlargement of the thyroid gland also increased steadily but even in the highest level of +16% or more (the average was +27.9%), where thyrotoxicosis was probably the main cause of the elevated metabolism, the thyroid enlargement was present only to the extent of 21.4% of the group. Exophthalmos was likewise of low incidence, and reached 7.1% of the group. Exophthalmos was likewise of low incidence, and reached 7.1% at the highest average metabolic level.

The incidence of overweight was greatest in the basal metabolic level of −15 to −6%, where it reached a level of 38.3%. Oddly enough, at a lower level of metabolism, the incidence was only 22.3%. Above the metabolic level of −15 to −6% there was a steady decline in the incidence of overweight. The fact is often overlooked that in individual cases, high levels of basal metabolism may be and frequently are associated with gross overweight. In this series the group having the highest level still showed an overweight incidence of 22.9%. The highest incidence of *normal* weight (not depicted in the chart) was 80%, and was found at the lowest metabolic level. Thereafter the percentages were between 53 and 70

and showed no definite trend. The underweight group increased irregularly from the lowest to the highest level of basal metabolism.

Among the subjective symptoms, palpitation did not become unduly evident until the highest level of basal metabolism was reached, where 8.6% of the series complained of this symptom. Tremors became a pronounced symptom only at the abnormally high levels, where the maximum was 28.6%. "Nervousness" followed the same trend as did the tremors. Undue fatigue was most noticeable at the lowest level of basal metabolism where it was present in 26.4% of the series. It showed a marked decline to a minimum of 7.4% in the +6 to +15% level, from which point it began to show an upward trend. It is probable that a series with larger numbers of abnormally high metabolic rates would show a still further elevation in this symptom.

In addition to the basal rates (which represent heat production *per unit of body surface* in percentage of normal), a study has been made of the same list of symptoms and findings with reference to the total resting metabolism (total heat production) in that portion of the thousand whose basal rates were between −10 and +10% of normal. It is perhaps not sufficiently well recognized that there is a difference between basal metabolism as reported by the laboratory and the total resting metabolism. This distinction has been emphasized previously.[2] It should be borne in mind that whereas "basal" metabolism represents only the unit heat production, the total metabolism represents the heat production of the body as a whole, both expressed in percentage of normal. These percentages will be identical when the weight is normal. In case of overweight the total resting metabolism will exceed the basal metabolism directly as the degree of overweight. An increased surface area means a greater total heat production even though the unit heat production is within normal limits. The distribution of the 630 cases with basal rates of −10 to +10% is shown in Table 2.

TABLE 2.—DISTRIBUTION ACCORDING TO TOTAL RESTING METABOLISM OF 630 CASES WITH BASAL RATES OF −10 TO +10% OF NORMAL.

Group.	Males.	Females.	Total.	Average T.H.P., %.
−6% or less	53	73	126	− 9.1
−5 to +5%	119	170	289	− 1.0
+6 to +15%	58	96	154	+ 9.6
+16% or more	16	45	61	+21.3

It has been stated by Evans and Strang[1,3,4] that there are frequently found in the obese many of the signs which are associated with the high basal metabolic levels of hyperthyroidism, since the rate of total heat production is elevated. However, the frequency with which various signs and symptoms make their appearance was not stated. Our study includes only those individuals whose basal metabolisms were within normal limits, but many of whose

total heat productions were distinctly increased. The results of this study are set forth in Chart 2.

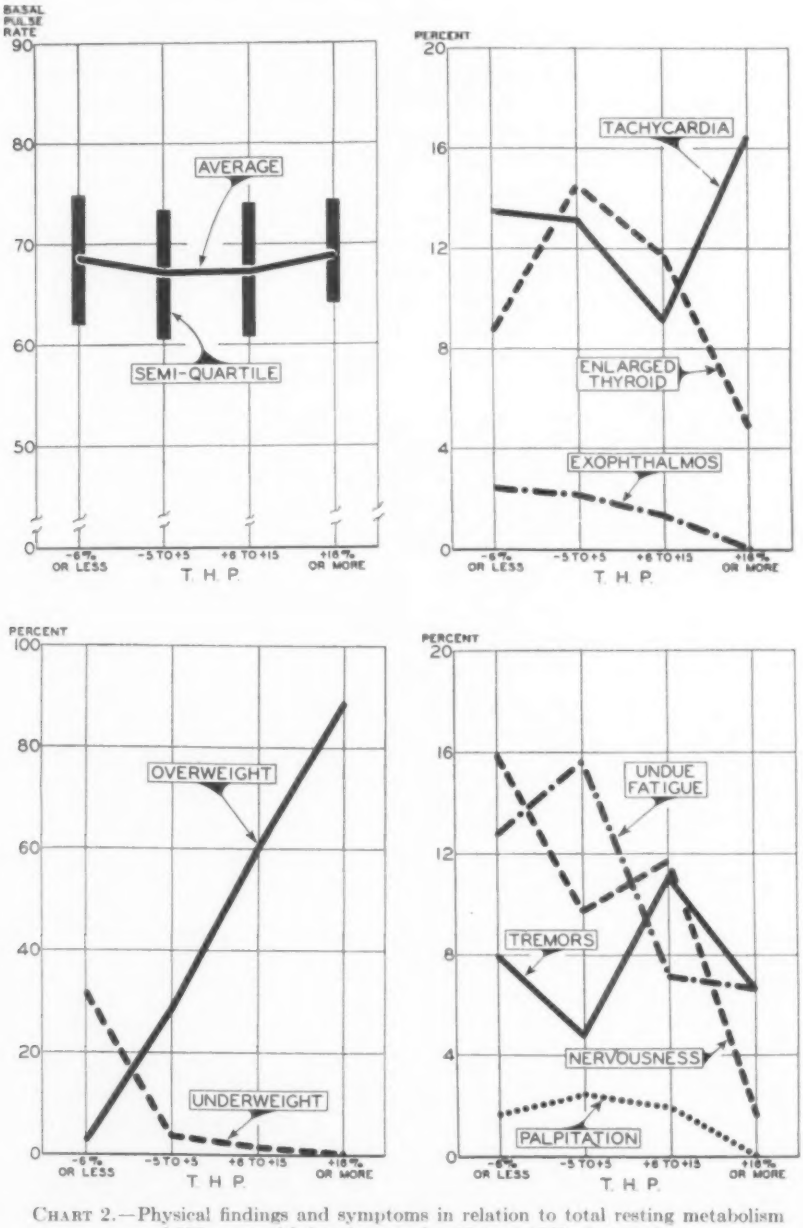


CHART 2.—Physical findings and symptoms in relation to total resting metabolism of 630 cases with basal rates of -10 to $+10\%$ of normal.

In view of the statements by Evans and Strang[1,3,4] and the experience of the writer, it was expected that there would be found in the study of the total resting metabolic rates a picture somewhat similar to that presented by the basal metabolic rates. Definitely abnormal basal metabolic rates were excluded in order to eliminate their influence upon the total heat production.

As we study the incidence of signs and symptoms in Chart 2, it is evident that the same trends found in Chart 1 are not present. Average pulse rates were almost the same at the various levels of total heat production with no definite trend manifest. The incidence of tachycardia which first showed a decline in the three lower levels increased sharply at the highest level which represented the greatest degree of overweight. The incidence of enlarged thyroid was the reverse of that seen in Chart 1, as was also the incidence of exophthalmos.

There was of course a very definite, sharp upward trend in the incidence of overweight, simply because the increase in total heat production, where the basal metabolic rate is normal, depends upon the presence of overweight.

Undue fatigue declined sharply from the lowest level to the highest as did also the incidence of "nervousness." Tremors were irregular and showed no definite trend. Palpitation was less evident at the highest level.

It is evident that relevant signs and symptoms in this series did not follow the trends at different rates of *total resting* metabolism that were seen at the same levels of *basal* metabolism when the cases with abnormal basal rates were excluded. It is possible in a series having more pronounced degrees of overweight which would of course show still larger increases in the total heat production, that a greater trend toward abnormal signs and symptoms would be manifested. In this study, however, there were no similar trends in physical signs and subjective symptoms in association with increasing degrees of total resting metabolic rate levels.

Summary and Conclusions. 1. Pulse rates together with the incidence of tachycardia, enlarged thyroid, exophthalmos, overweight, underweight, tremors, undue fatigue, "nervousness" and palpitation have been studied in association with different levels of basal metabolic rate in a series of 1000 cases.

2. Pulse rates, tachycardia, thyroid enlargement, exophthalmos, "nervousness," tremors, palpitation and underweight increased in varying degrees with increasingly higher levels of basal metabolic rate, while fatigue and overweight showed predominantly an opposite trend.

3. Contrary to expectations the same trends were not found in association with increasingly higher levels of total resting metabolism. Although such pertinent findings and symptoms may be

prevalent in individual cases, particularly of the more obese type, they were not found to be generally characteristic.

Acknowledgment is made to Dr. H. J. Johnson who first suggested the value of this study, and to Miss M. F. Kelley and Mr. H. A. Ley, Jr., who did much of the statistical work.

REFERENCES.

(1.) **Evans, F. A.**, and **Strang, J. M.**: Am. J. Med. Sci., **177**, 339, 1929. (2.) **Short, J. J.**, and **Johnson, H. J.**: J. Am. Med. Assn., **106**, 1776, 1936. (3.) **Strang, J. M.**, and **Evans, F. A.**: J. Clin. Invest., **6**, 277, 1928. (4.) **Strang, J. M., McCluggage, H. B.**, and **Evans, F. A.**: Am. J. Med. Sci., **179**, 687, 1930.

PROTHROMBIN STUDIES IN PULMONARY TUBERCULOSIS.*

By J. W. Savacool, M.D.,

ASSISTANT DEMONSTRATOR OF MEDICINE, JEFFERSON MEDICAL COLLEGE, PHILADELPHIA, PA.

(From the Department for Diseases of the Chest, Jefferson Hospital.)

In the study of tuberculous patients, various laboratory tests for determining the degree of resistance and toxemia and of estimating the response to treatment have been employed. As yet no single laboratory method has proven satisfactory for this purpose. Of the procedures used, the erythrocyte sedimentation rate, the leukocyte index (Schilling) and the leukocyte-monocyte ratio (Medlar) have been the most widely used. At times certain conclusions can be drawn from a combination of such tests, particularly in objectively confirming clinical impressions regarding toxicity and reaction to treatment. In the present study an attempt is made to evaluate a comparatively new method which may be of aid in this connection.

The prothrombin coagulation time of the blood plasma has been extensively applied in the study of blood dyscrasias and hemorrhagic disorders in which prothrombin deficiency might be a factor. It has been fairly well established that the liver is essential for the maintenance of normal prothrombin values[2,3] and probably is the chief site of formation of prothrombin.[8] Other implications have been suggested, including the possibility that prothrombin activity might serve as an index of liver function and Wilson[9] has noted that it frequently parallels the hippuric acid excretion test for liver function. However, it is hardly conceivable that prothrombin determination would be a satisfactory method of evaluation of all the functions of the liver even though it is a sensitive reflector of liver damage in diseases directly involving the liver.[9] At the same time it is possible that changes may occur in the blood stream itself which might affect the circulating prothrombin without directly

* A part of the expense of this study was defrayed by a grant from the Joseph V. Horn Fund.

influencing its production in the liver. The present study suggests this possibility.

Material and Method. With the above consideration in mind the present study was undertaken for the purpose of determining what changes, if any, occur in the prothrombin of the plasma in pulmonary tuberculosis in various stages of the disease. Seventy tuberculous patients have been studied. There are included a number of patients who have undergone collapse therapy, either artificial pneumothorax or thorocoplasty, some early cases prior to active treatment and some far advanced cases with either progressive caseating lesions or chronic fibro-ulcerative lesions. Several patients with such complications of artificial pneumothorax as tuberculous and mixed infection empyema are included.

The procedure for determining the prothrombin of the blood plasma consists of the quantitative method of Quick,[6] in which oxalated plasma is recalcified in the presence of tissue thromboplastin obtained from rabbit brain. The thromboplastin solution is prepared by centrifugation from a thymolized normal saline suspension and standardized each time it is used by means of three normal control subjects. The results are reported in percentage of average normal. In many instances several determinations were made in the same patient, particularly when a change in the treatment was undertaken or when some alteration in the clinical course occurred. The erythrocyte sedimentation rate and vital capacity were determined for each patient. Complete clinical studies including routine chest Roentgenograms and leukocyte counts were carried out in all patients.

Findings. For statistical analysis, the patients are divided according to the prothrombin values into 4 arbitrary groups (Table 1), the first composed of those having a prothrombin value of over 100%, the second from 80% to 99%, the third from 60% to 79% and the fourth less than 60%. Group 1 includes 16 patients. Of these, 12 were patients who had had a satisfactory pneumothorax or thoracoplasty and the disease was almost or completely under control. Two patients had old inactive, fibrotic lesions with negative sputum who could not be considered as definitely arrested but who were quiescent. The other 2 had partly effective pneumothorax with symptomatic and clinical improvement but without completely controlling the disease. One (R.P.) subsequently developed a spontaneous pneumothorax followed by a tuberculous effusion and when this occurred there was a sharp drop in the prothrombin level from 150% to 49%.

In Group 2, there were 22 patients. Of these, 11 had pneumothorax but only 2 of these had completely controlled tuberculosis, the others having been early cases of pneumothorax or patients with active disease in the opposite lung. Seven had some form of surgical collapse but 6 were considered as still having active disease. Two had low-grade activity with partial collapse by pleural effusion and 2 had long-standing chronic fibrotic tuberculosis with an essentially benign clinical course. One patient included in this group (E.L.) developed tracheal lesions and reactivation of an apparently quiescent focus in the left lung with a drop in the prothrombin value from 85% to 70%. Another (F.K.) had an unsatisfactory

pneumothorax, the abandonment of which resulted in a decrease of the prothrombin activity from 85% to 64%.

TABLE 1.—COMPOSITE RECORD OF RESULTS INCLUDING SEDIMENTATION TIME AND VITAL CAPACITY.

Case.	Date,* 1940.	Quantitative prothrombin. Control time.	Patient's time.	%	V.C.	Sed.† rate.	Clinical condition.
			Group 1.				
W.K.	9/21	15.5	14.1	180	2800	7	Thoracoplasty with arrest; working.
M.H.	7/19	20.5	19.3	165	1500	30	Old fibrotic type; negative sputum.
G.T.	3/26	14.5	13.4	160	3100	4	Good pneumothorax; cavity closed.
R.P.	4/12	16.5	15.6	150	3000	20	Early pneumothorax; cavity open.
	9/18	16.0	19.7	49	1500	30	Following spontaneous pneumothorax with tuberculous effusion.
M.G.	9/21	15.5	14.6	150	900	12	Old fibrotic type; negative sputum.
C.L.	4/12	16.5	15.7	145	900	9	Thoracoplasty and apparent arrest.
E.T.	9/9	19.0	18.4	135	1400	7	Thoracoplasty; low-grade activity.
J.S.	9/13	20.5	19.9	135	3500	6	Good pneumothorax; working.
K.S.	4/12	16.5	15.9	132	1000	22	Extrapleural pneumothorax; sputum neg.
M.T.	4/12	16.5	16.1	120	800	10	Bilateral pneumothorax; sputum neg.
M.W.	4/5	16.5	16.3	110	1000	28	Early pneumothorax.
M.H.	9/27	16.5	16.3	110	1000	9	Thoracoplasty, almost quiescent.
A.F.	4/2	14.0	13.7	105	1300	8	Good pneumothorax; sputum neg.
J.K.	3/26	14.5	14.4	105	2700	6	Good pneumothorax; working.
M.O.	3/29	14.0	14.1	100	1200	21	Thoracoplasty for tuberculous empyema.
W.S.	4/19	16.0	16.0	100	2400	9	Pneumothorax, partial control, sputum.
			Group 2.				
A.C.	3/23	14.5	14.7	98	1700	8	Good pneumothorax; working.
F.A.	9/18	16.0	16.4	96	3000	12	Early pneumothorax; disease controlled.
M.H.	4/9	15.5	15.8	95	1400	5	Good pneumothorax; sputum negative.
M.K.	4/5	16.5	16.8	95	800	18	Fibrotic type, low grade; phrenic.
M.K.	9/19	19.0	19.5	93	1500	25	Early pneumothorax; cavity open.
K.M.	4/9	15.5	16.0	93	600	29	Extrapleural pneumothorax; active.
F.W.	3/26	14.5	15.2	90	1900	6	Good pneumothorax; working.
L.S.	10/21	17.0	17.5	92	2400	22	Chronic fibroid type; sputum positive.
M.P.	4/9	15.5	16.1	91	2100	30	Chronic fibroid type; sputum positive.
F.W.	4/5	16.5	17.1	91	1600	30	Pneumothorax; opposite side active.
D.I.	4/11	16.5	17.2	90	1500	23	Pneumothorax and thoracoplasty.
E.H.	9/9	19.0	19.7	90	1670	25	Early pneumothorax.
P.C.	3/26	14.5	15.2	90	1700	27	Hydropneumothorax; sputum negative.
L.W.	4/2	14.0	14.7	89	1300	25	Clearing tuberculous empyema.
B.C.	3/26	14.5	15.3	89	1800	21	Thoracoplasty, low-grade activity.
M.O.	4/2	14.0	14.9	87	1000	25	Pneumothorax; opposite side active.
H.L.	4/2	14.0	14.9	87	950	15	Pneumothorax and thoracoplasty.
E.M.	4/5	16.5	17.5	85	2100	30	Low-grade activity, mod. advanced.
E.L.	4/9	15.5	16.5	85	1700	15	Right pneumothorax; left fibrosis.
	10/18	19.0	21.1	70	1200	23	Tuberculous tracheitis developed.
F.K.	4/9	15.5	16.5	85	800	32	Rt. thoracoplasty; left pneumothorax.
	10/11	19.0	21.5	64	1300	30	Left lung reëxpanded; open cavities.
M.A.	3/23	14.5	15.5	85	1500	3	Thoracoplasty; low-grade activity.
T.C.	3/26	14.5	15.8	81	1700	15	Thoracoplasty for tuberc. empyema.
			Group 3.				
I.L.	10/2	17.0	18.5	79	2000	8	Early pneumothorax; incomplete collapse.
L.M.	4/4	14.0	15.6	79	800	21	Right pneumothorax; left open cavity.
L.W.	9/18	16.0	17.5	78	2800	18	Spontaneous pneumothorax; pleurisy.
A.D.	4/19	16.0	17.6	77	1200	25	Far advanced active tuberculosis.
H.H.	4/18	16.0	17.6	77	1700	29	Tbc. empyema; bronchopleural fistula.
F.H.	3/26	14.5	16.1	76	1800	21	Far advanced active tuberculosis.
L.F.	3/26	14.5	16.2	75	1500	28	Tbc. empyema; pleurocutaneous fistula.
C.M.	7/19	20.5	22.3	74	1300	7	Postoperative thoracoplasty.
F.G.	10/8	16.5	18.6	70	3700	13	Early tuberculosis with hemoptysis.
	10/25	18.0	16.1	225	3700	13	Hemoptysis stopped; cavity previously seen no longer apparent.
M.A.	9/27	16.5	18.6	70	850	30	Far advanced active tuberculosis.
J.M.	3/23	14.5	16.7	69	1000	12	Tbc. empyema; thoracoplasty.
E.T.	9/9	19.0	21.2	68	2300	26	Active fibroid tuberculosis; cavity.
R.A.	4/9	15.5	17.8	67	1500	26	Pneumothorax; opposite side active.
A.T.	9/21	15.5	17.7	66	2600	32	Early chronic exudative tuberculosis.
M.B.	3/29	14.0	16.6	63	2300	27	Early chronic exudative tuberculosis.
A.H.	7/12	18.0	20.7	61	2100	25	Far advanced fibroid tuberculosis.
J.S.	7/12	18.0	20.7	61	1900	25	Far advanced ulcerative tuberculosis.

Case.	Date,* 1940.	Quantitative prothrombin. Control time.	Patient's time.	%	V.C.	Sed.† rate.	Clinical condition.
			Group 4.				
G.O.	3/23	14.5	17.4	59	1800	24	Tbc. empyema; opposite side active.
H.W.	3/23	14.5	17.4	59	1900	11	Exudative tuberculosis; hemoptysis.
I.L.	10/8	16.5	19.8	53	1600	29	Far advanced tuberculosis; effusion.
H.H.	3/23	14.5	17.7	53	2000	17	Right thoracoplasty; left pneumothorax.
C.M.	9/13	20.5	23.9	51	2100	30	Right pneumothorax; activity on left.
C.M.	3/29	14.0	17.4	51	1600	30	Mixed infection empyema.
P.B.	7/12	18.0	21.5	50	3100	30	Pulmonary and urogenital tuberculosis, far advanced.
S.E.	10/2	17.0	20.8	49	1600	18	Chronic fibroid tuberculosis, atelectasis.
C.S.	10/11	19.0	23.0	48	700	30	Chronic fibroid tuberc. and atelectasis.
A.C.	9/13	20.5	24.9	47	1800	25	Acute pleurisy with hemorrhagic effusion.
M.V.	7/12	18.0	22.5	47	1600	15	Pneumothorax; hemoptysis.
J.T.	10/18	19.0	23.5	46	2800	24	Exudative tuberculosis with hemoptysis.
M.G.	10/8	16.5	21.3	45	1100	22	Exudative tuberculosis on left side.
	10/18	19.0	21.2	68	700	22	Pneumothorax started on left.
W.P.	10/2	17.0	23.4	40	2500	28	Bilateral chronic active tuberculosis.
M.R.	4/5	16.5	24.1	36	800	26	Far advanced bilateral tuberculosis with atelectasis.

* Dates given are for prothrombin determinations.

† In some instances, dates of sedimentation and vital capacity determinations do not exactly coincide with those of prothrombin determinations. Sedimentation recorded in millimeters in 1 hour.

There were 17 patients in Group 3. Seven of these had thoracoplasty with the activity not yet controlled and of these, 3 had tuberculous empyema. Four had pneumothorax with persistent pleurisy or activity in the opposite lung. Five had far advanced disease without collapse therapy. One was an early case with hemoptysis (F.G.). Following complete rest in bed during which time the hemoptysis was controlled and the lesion showed signs of clearing, there was a marked increase in the prothrombin from 70% to 225%.

Group 4 was made up of 15 patients. There were 8 with far advanced active disease with unsatisfactory or no collapse or with activity in the opposite lung. Most of the patients with acute caseous tuberculosis were found in this group. Three patients had hemoptysis and 2 of them had active disease with positive sputum. One had severe pleurisy with a bloody effusion and one had thoracoplasty on the right with artificial pneumothorax on the left. Two had empyema, 1 tuberculous and 1 mixed infection. One patient (M.G.) who, 6 years previously, had a right thoracoplasty, developed a widespread and fairly acute type of disease in the left lung. The prothrombin was 45% and 1 week after initial pneumothorax on the left side the value was 68%.

The sputum studies in the 4 groups (see Table 1) are indicated in Table 2, showing the relationship between the patients with positive sputum and the prothrombin values. In Group 1, with normal or increased prothrombin values, only 31% had positive sputum and in Group 4, with markedly decreased prothrombin values, 87% were positive. In Groups 2 and 3, 78% and 83% respectively had positive sputum, showing the tendency toward progressively lowered prothrombin values in the groups with more active disease.

The sedimentation rate and vital capacity determinations have been included in Table 1, in order to point out the relationship

between those values and the prothrombin levels. It is found that in Group 1 the sedimentation is normal in all patients who are considered arrested and who are employed. A few in whom the prothrombin was above normal showed sedimentation rates slightly more rapid than normal. This was particularly true of the patients with early pneumothorax or thoracoplasty in whom the disease was not under control. One patient (W.S.) had a normal sedimentation rate and 100% prothrombin but still had active tuberculosis with unsatisfactory collapse. In Group 2, the sedimentation rates of all the patients were rapid with the exception of the 3 with good pneumothorax (M.H., A.C., F.W.) who were in this group and the 1 patient (T.C.) who had just recently had a three-stage thoracoplasty for tuberculous empyema. In Group 3, most of those with active tuberculosis had rapid sedimentation rates but 2 who had pneumothorax or thoracoplasty had normal values. In Group 4, the sedimentation time was rapid in all except 2 cases and both of these were patients with hemoptysis, one with active disease (H.W.) and the other with pneumothorax (M.V.) and hemoptysis with no evidence of active disease. In the latter case the hemoptysis was believed to have resulted from bronchial changes of a mechanical nature related to the pneumothorax. It appears from these findings that the sedimentation rates and the prothrombin values parallel each other but there are enough variations both ways to rule against drawing any positive conclusions from either test.

TABLE 2.—SPUTUM STUDIES OF PATIENTS IN GROUPS OF TABLE 1.

	Positive sputum.		Negative sputum.	
	No.	%.	No.	%.
Group 1	5	31	11	69
Group 2	17	78	5	22
Group 3	14	83	3	17
Group 4	13	87	2	13

The reduction of vital capacity is not alone responsible for the increased prothrombin level in the tuberculous patients in whom this condition was present. Reference to Table 1 shows that there are many patients with low vital capacities who at the same time have decreased prothrombin values. Most of these have incompletely effective collapse or persisting toxicity from other causes.

Discussion. From a study of the findings, certain trends become apparent. It is noted that the patients who have effective collapse therapy have a normal or increased prothrombin level and in those with partly successful collapse treatment the values approach normal except in the presence of such complicating factors as activity in the opposite lung, pleurisy, tuberculous empyema or hemoptysis. The patients with low-grade activity or chronic

fibrotic tuberculosis also show prothrombin values which approach normal. On the other hand, the patients with the more severe or acute forms of pulmonary tuberculosis tend to have low values, while those with chronic ulcerative lesions have moderately reduced values. In the chronic ulcerative cases with early or unsatisfactory collapse treatment, the prothrombin approaches normal even if the disease is not adequately controlled.

One of the most interesting observations is the increased rapidity of prothrombin clotting in the effective collapse therapy group. A possible explanation of this finding is suggested by the studies of Andrus *et al.*[1] who found a fall in prothrombin activity in the blood coming from the lungs of dogs as compared with that entering the lungs. No such fall was noted between the blood entering and leaving any other organ. They suggest the conclusion that prothrombin is destroyed in the lungs. If this is the case, collapse therapy might sufficiently alter the character and rate of circulation through the lungs to affect significantly the destruction of prothrombin. The reduction in circulation in a collapsed lung has been previously discussed[4,5] and is accepted as one of the effects of collapse therapy. It is quite conceivable that this circulatory change could prevent the destruction of prothrombin which normally occurs in the lungs according to present evidence.

There is no definite parallelism between the degree of collapse and the actual prothrombin value, a small amount of collapse producing the same increase in prothrombin as a marked collapse, provided the lesions are under control. This again is probably dependent upon the circulatory physiology of collapse therapy, a rather marked reduction in circulation which is out of proportion to the reduction in vital capacity taking place soon after the lung is collapsed.

In the patients with active disease with diminished prothrombin, other factors probably play a large part. The fact that the reduction of vital capacity is not always associated with increased prothrombin values strongly supports this conclusion. Of these factors, toxemia appears to be most important and it appears from a study of the patients in Groups 3 and 4 that the decrease in prothrombin is almost directly proportional to the degree of toxemia. The decreased toxic absorption which occurs in collapse therapy has often been observed clinically and probably is associated with the decreased circulation and decreased æration of the lung which may have a deleterious effect on the tubercle bacilli. The increase in the rapidity of prothrombin clotting in collapse therapy suggests that the toxins may have played a part in decreasing the amount of prothrombin. It may even suggest that the toxic products themselves have a destructive effect on the circulating prothrombin.

The relationship between prothrombin and activity of the tuberculous process is further suggested by the sputum examinations. Table 2 indicates the progressive increase in the number of patients with positive sputum from Group 1 to Group 4. Most of the patients with negative sputum appear in Group 1, a few in Group 2 and very few in Groups 3 and 4. The importance of this finding becomes apparent when coupled with the other observations.

To determine whether the prothrombin deficiency in the patients with far advanced disease responds to vitamin K, 3 patients (H.H., I.L., C.S.) were given oral treatment with 2-methyl-1, 4-naphthoquinone. Doses up to 6 mg. daily were used and the prothrombin checked repeatedly. In none of the cases studied was any increase in prothrombin noted as a result of the therapy.

Of special interest are the patients with hemoptysis. Several patients with this symptom had fairly low prothrombin values (59%, 47%, 46%) but none of these appeared to be ill enough to account for such a marked decrease in prothrombin as compared with other patients in the group. The sedimentation rate was not as rapid in these patients as in others with comparable prothrombin levels. It is thus possible that the hemoptysis had something to do with the low prothrombin values. On the other hand, it is unlikely that the low prothrombin values could have been responsible for the hemoptysis from a standpoint of clotting deficiency, with the possible exception of the last patient in Group 4 (M.R.) who died during a massive hemoptysis. The last determination about 2 weeks before death revealed a prothrombin level of 36%. She was extremely toxic with tuberculous tracheobronchitis, bronchial stenosis and atelectasis and this may have accounted for sufficient decrease in prothrombin to prevent formation of a clot when a small vessel was eroded. In the patient with early tuberculosis (F.G.) who showed marked increase in prothrombin following cessation of the hemoptysis, an overcompensatory mechanism is suggested.

Since this study was undertaken, there have been several instances in which the prothrombin determination was of assistance in evaluating the clinical status of patients under consideration for collapse therapy. For example, the patient with hemoptysis in Group 3 (F.G.) was considered for artificial pneumothorax and it was found that his prothrombin had undergone a marked increase following rest in bed and cessation of the hemoptysis. Accordingly stereoscopic Roentgen films were made which revealed closure of the cavity previously seen in the right apex and for this reason collapse was deferred. Because of these considerations it is suggested that the method of prothrombin determination be applied in the study of tuberculous patients particularly when there is a question of cavity closure, activity of the disease or effectiveness of collapse

therapy and when changes in treatment are under consideration. For purposes of investigation the quantitative method appears to be most accurate, but in actual use this may be modified by one of the bedside methods.[10] The Quick method would be simplified if the "lyophilized" thromboplastin becomes available for general use.[7]

Conclusions. 1. Prothrombin determinations are reported on 70 patients with pulmonary tuberculosis.

2. In general, there is an increase in prothrombin in patients in whom the disease is controlled, particularly those with effective collapse therapy. The possible relation of this phenomenon to the destruction of prothrombin which may take place in the lungs is considered.

3. The patients with very active disease show a marked diminution in prothrombin activity, while those with chronic disease of moderate activity or early collapse therapy show a less marked decrease. As clinical improvement occurs, there is a gradual increase in the circulating prothrombin. The possibility of toxic absorption in this connection is discussed.

4. The sedimentation rate of erythrocytes does not always run parallel to the prothrombin level and the variation is not entirely constant. In a general way, however, the prothrombin level appears to give more information concerning the clinical status than the sedimentation rate.

5. The vital capacity bears no definite relation to the prothrombin level, but when the disease is completely inactive there is usually an increase in prothrombin when reduction in the vital capacity occurs.

6. Hemoptysis appears to be associated with a decrease in prothrombin beyond that expected from the stage of advancement of the disease or the toxicity.

7. It is suggested that toxemia may play a part in the diminished prothrombin in patients with active tuberculosis.

8. The inclusion of prothrombin determination in the study of patients with tuberculosis is proposed.

The suggestions and criticism of Drs. Burgess Gordon and L. M. Tocantins are hereby acknowledged.

REFERENCES.

(1.) **Andrus, W. DeW., Lord, J. W.**, and **Kauer, J. T.**: Science, **91**, 48, 1940. (2.) **Andrus, W. DeW., Lord, J. W.**, and **Moore, R. A.**: Surgery, **6**, 896, 1939. (3.) **Brinkhous, K. M.**: Medicine, **19**, 329, 1940. (4.) **Carvalho, L.**, and **Carvalho, A.**: Rev. de la tuberc., **1**, 578, 1935. (5.) **Charr, R.**, and **Savacool, J. W.**: Arch. Path., **30**, 1159, 1940. (6.) **Quick, A. J.**: Am. J. Clin. Path., **10**, 222, 1940. (7.) **Souter, A. W.**, and **Kark, R.**: Am. J. Med. Sci., **200**, 603, 1940. (8.) **Warner, E. D.**: J. Exp. Med., **68**, 831, 1938. (9.) **Wilson, S. J.**: J. Lab. and Clin. Med., **25**, 1139, 1940. (10.) **Ziffren, S. E., Owen, C. A., Hoffman, G. R.**, and **Smith, H. P.**: Proc. Soc. Exp. Biol. and Med., **40**, 595, 1939.

THE SURVIVAL TIME AFTER TRANSFUSION OF ERYTHROCYTES OF CITRATED HUMAN BLOOD STORED AT 4° TO 6° CENTIGRADE.

By William P. Belk, M.D., F.A.C.P.,
DIRECTOR OF LABORATORIES,

AND

B. C. Barnes, M.D.,
RESIDENT PATHOLOGIST,
THE EPISCOPAL HOSPITAL, PHILADELPHIA, PA.

An *in vitro* study made in this laboratory[2] of the keeping properties of chilled citrated human blood showed that the red cells became fragile, and began to hemolyze, near the end of the first week of storage. Clinical observations in which multiple transfusions failed to elevate hemoglobin as expected suggested that these cells were rapidly destroyed in the patients' circulation.

In 1919 Ashby[1] described a method for determining the life of transfused cells. This consists, in brief, of transfusing recipients of blood groups AB, A or B with O blood and making red cell counts with O plasma as diluting fluid. The O plasma clumps the cells of the recipient, leaving those of the donor to be counted as unagglutinated cells. This method, slightly modified, was made use of in the present study. We used a red cell rather than a white cell pipette, as the lower concentration of cells seemed to permit more accurate counting. The 1-hour incubation at 37° C. was omitted, and the storage over night in the refrigerator was effected in the diluting pipette rather than in a test tube into which Ashby blew the blood-plasma mixture. Attempts at more radical modification, especially omission of the period of chilling, gave erratic results. All counts were made in duplicate, 160 small squares being counted for each. Only cells which were completely separated from all others were recorded. The variation between single counts was about 25%, and the average of the two was considered accurate to about 15%, which is the error in ordinary red cell counting.

All individuals have, naturally, some inagglutinable cells. The number varies considerably, being most often under 100,000; but extremes of 215,000 and 10,000 were noted in our studies. This number was determined for each individual immediately prior to transfusion. The difference between this and inagglutinable cell counts made subsequently gave the number of donor cells present in the patient on the various days of observation. Such observations, were, as a rule, made daily, some counts being at longer intervals in cases of prolonged survival. The amount of blood given in most instances was 500 cc.

Investigations were made, all told, on 25 subjects. In 11 of these, because of death, discharge from the hospital, additional trans-

fusions with O blood, or other reasons, studies were not satisfactorily concluded. Individual records of 11 of the 14 completed observations are illustrated in Chart 1. The numbers at the end of the lines represent the days each blood was kept in the refrigerator prior to transfusing it. Observations on the 2-day-old blood were discontinued before the cells had entirely disappeared. Two liberties were taken in transferring the data to the charts. In the case of the 5-day-old blood the count reached 150,000 cells on the 20th day, then remained at this level for approximately 3 months. Since several subjects had inagglutinable counts greater than this prior to transfusion, this record was considered terminated on the 20th day. Likewise the record of the 6-day-old blood showed so little change between the 20th and the 48th days that it was regarded as terminated at the earlier date. This has reduced the scatter of observations on Chart 2, but we feel that the line as drawn more nearly represents the truth of the matter.

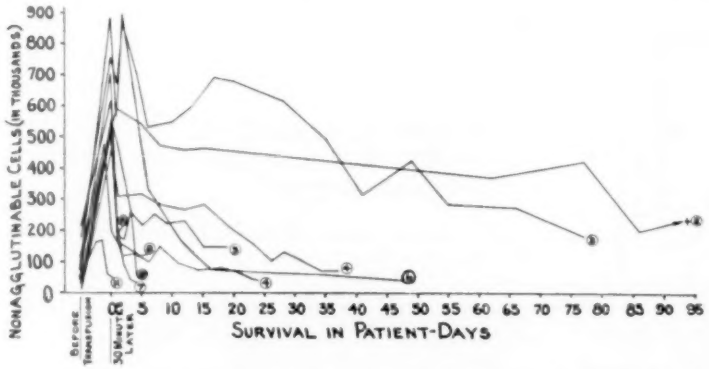


CHART. 1.—Erythrocyte survival after transfusion of stored citrated blood (agglutination method).

Chart 1 tells its own story. There is a sharp rise in the number of inagglutinable cells immediately after transfusion, then a gradual fall as the cells disappear from the circulation. The red cells of the 2- and 3-day-old blood survived as long as did those of fresh blood in Ashby's and Wearn's[8] studies. As storage time lengthens survival time decreases.

This inverse relationship between storage time and survival time is more clearly shown in Chart 2. This chart is constructed by plotting the number of days during which the bloods were stored against the number of days donors' red cells could be detected in the recipient's circulation. The curve indicates that bloods stored no longer than 2 or 3 days are retained by the recipient, and presumably used by him for long periods. There occurs then a rapid shortening of the survival time of these cells as storage time length-

ens, until, after 7 or more days of storage, the donors' erythrocytes are eliminated in 1 or 2 days.

Additional evidence of rapid destruction of red cells was sought by means of the icterus index and tests for hemoglobin and increase of urobilin in the urine. This was done on 13 of the patients recorded in the charts, and on 21 others. There was, in fact, a moderate increase in blood pigment and in urobilin in some of the instances where old blood was used, and in 2 hemoglobinuria was noted. This correlation, however, was by no means a close one. In this connection it may be mentioned that a higher incidence of jaundice following transfusions of stored rather than of fresh blood has been noted by Fox,[4] Brewer *et al.*[3] and by us.[2] The absence of jaundice, urobilinuria and hemoglobinuria in some instances of rapid destruction of transfused erthrocytes is probably accounted for by a greater capacity on the part of the endothelial cells and the liver of certain individuals to handle diffused hemoglobin. It is of some importance

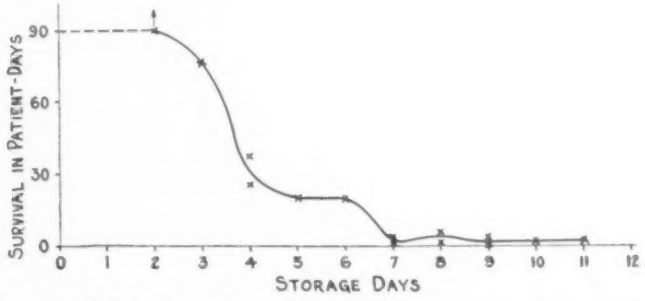


CHART 2.—Relation between storage time and survival of erythrocytes after transfusion.

to appreciate that an absence of the clinical evidences of hemolysis is not proof that hemolysis has not occurred. Failure to appreciate this probably accounts for the numerous expressions in medical literature of satisfaction with "bank" blood, some of it quite old.

Our results with counts of inagglutinable cells are supported by the work of Wiener and Schaefer[6] who followed the disappearance of transfused erythrocytes with the use of M and N agglutinogens. In their observations the deleterious effect of storage appeared later than in our bloods, prolonged survival being noted up to about the 8th day. After this the curve of shortening intravascular life was similar to ours, but more gradual. The fact that observations were usually made at weekly rather than daily intervals may account in part for this difference.

The demonstration of rapid deterioration of stored citrated blood for transfusion should be of benefit to those interested in "blood banks." The original proponents of this method advocated an upper age limit for stored blood of 14 days. We have used this

limit, and the average storage age of blood in all our 1480 transfusions has been 6 days. We find it unpleasant, now, to realize what relatively worthless material we have been supplying many of our patients in the belief that they were receiving whole blood transfusions.

Conclusion. The erythrocytes of citrated human blood kept at 4° to 6° C. were found to survive in recipients as long as do the cells of fresh blood when storage time did not exceed 2 or 3 days. After this they disappeared with increasing rapidity as storage time increased, until, after 7 or more days in the "bank," their post transfusion survival was in no case longer than 24 or 48 hours.

The authors wish to express appreciation for the coöperation on the part of the Chiefs of the Medical and Surgical Services of this Hospital in making this study possible.

REFERENCES.

(1.) **Ashby, W.**: J. Exp. Med., **29**, 267, 1919. (2.) **Belk, W. P., Henry, N.**, and **Rosenstein, F.**: Am. J. Med. Sci., **198**, 631, 1939. (3.) **Brewer, H. F., Maizels, M., Oliver, J. O.**, and **Vaughn, J.**: Brit. Med. J., **2**, 48, 1940. (4.) **Fox, H.**: Pennsylvania Med. J., **43**, 49, 1939. (5.) **Wearn, J. T., Warren, S.**, and **Ames, O.**: Arch. Int. Med., **29**, 527, 1922. (6.) **Wiener, A. S.**, and **Schaefer, G.**: Med. Clin. North America, **24**, 705, 1940.

THE EFFECT OF GLUCOSE IN THE PRESERVATION OF CITRATED HUMAN BLOOD STORED AT 4° TO 6° CENTIGRADE.

By William P. Belk, M.D., F.A.C.P.,
DIRECTOR OF LABORATORIES,
AND
Florence Rosenstein, M.T.,
THE EPISCOPAL HOSPITAL, PHILADELPHIA, PA.

An *in vitro* study from this laboratory[2] of the keeping properties of citrated human blood stored at 4° to 6° C. showed the development of visible hemolysis in about 5 days, the rapid disintegration of granulocytes and of platelets, and a speedy decrease in clot forming properties. A subsequent *in vivo* study[1] by Ashby's method of the survival time in the recipient's circulation of red cells which had been stored for varying intervals demonstrated even more convincingly the rapid deterioration of chilled citrated erythrocytes. Up to 2 days of storage transfused cells could be detected in the recipient for 60 to 90 days, a survival period equal to that of fresh blood. Between the 2d and the 7th day the life of these transfused cells shortened rapidly, and after the 6th day all were destroyed by the patient in 24 to 48 hours. Quite clearly such "blood" is an almost worthless medium for whole blood transfusions, except in the largest institutions, where the turnover of the "bank" is complete every 2 or 3 days.

In 1916, Rous and Turner[8b] demonstrated that glucose greatly

delayed the hemolysis of rabbit erythrocytes stored in the ice-box, and that these cells, up to 2 weeks of storage, served to replace physiologically cells removed from this animal by bleeding. During the preparation of the present paper a number of reports have appeared showing this property of glucose to be effective in the preservation of human cells. Certain considerations, however, need more specific definition, particularly the optimum amount of glucose, and the length of time that such storage will, with certainty, keep blood in a highly usable state.

Methods. Blood from human donors was received into 20% solution of sodium citrate, dihydric, to make a final citrate concentration of 0.4%. The proper amount of glucose was added, gently mixed, and apportioned into 125 ml. Pyrex Erlenmeyer flasks. Flasks were capped with flask hoods and stored at 4° to 6° C. The volume of blood-citrate-glucose was, with one exception noted later, always the same, 30 ml., no matter what the proportions of each, so that the effect of glass contact was the same in all cases. A separate flask was prepared for each day's observation, so that the hemolytic effect of repeated agitation and of repeated warming and chilling was avoided.

Fragility was determined by shaking blood in an electric shaker for 5 minutes and centrifuging to show the color of the plasma, in addition to the usual method with saline dilutions. Hemolysis by inspection consisted of mixing the blood, then centrifuging a portion to show the color of the plasma. Quick's prothrombin time was done by the original method, except of course, that oxalate was not used. The estimation was controlled each day by a parallel determination on a normal blood, and corrected, by simple proportion, to 12 sec. = 100%. The hematocrit used was Wintrobe's; plasma chlorides were determined by the method of Wilson and Ball; phosphates, that of Fish and Subbarrow; potassium, Stahl and Bennett; glucose, Folin and Wu; carbon dioxide combining power, Van Slyke and Cullen, and oxygen capacity by the method of Van Slyke and Stadie.[10]

Our first series of observations, in addition to reassessing the preserving properties of glucose, was designed to show the minimum amount of 5.4% (isotonic) glucose which would be highly effective. This was for the obvious desideratum that the volume of fluid for infusion should be as small as possible. In addition, the administration of considerable quantities of glucose would be undesirable in diabetics. The effect on erythrocytes of varying the proportion of blood and glucose, 5.4%, from 2 to 1 to 10 to 1 is shown in Table 1.

It is seen that the larger the proportion of glucose to blood the better the preservation. This is in agreement with the observations of Rous and Turner,[8a] De Gowin,[3] and others. On the other hand, with even so small an amount of glucose as 1 part to 10 of blood, preservation, as compared with that of citrate alone, is clearly superior. The advantage gained by additional amounts of glucose is distinct, but relatively small. With 1 part of glucose to 2 of blood fragility of erythrocytes to saline is essentially unchanged, and hemolysis (shaking) is not present on the 21st day of storage. On the 28th day only slight hemolysis is present. Very probably

somewhat better preservation could be obtained by increasing the proportion of glucose to 1 to 1 or more. We feel, however, that the proportion of 2 parts of blood to 1 of glucose represents a practical adjustment of the 2 considerations; namely, effective preservation, and minimum volume of transfusion material. This technique too avoids the use of excessive quantities of citrate such as was employed by Rous and Turner, the actual amount being 2 gm. per 500 cc. of blood, or per 750 cc. of injection fluid. We have been using blood so stored for some time with complete satisfaction.

TABLE 1.—THE EFFECT OF VARYING PROPORTIONS OF 5.4% GLUCOSE ON THE FRAGILITY AND HEMOLYSIS OF ERYTHROCYTES OF WHOLE CITRATED HUMAN BLOOD KEPT AT 4° TO 6° C.

Proportion of blood to glucose.		Days: 0	7	14	21	28
B 2	F.S.	0.40	0.40	0.40	0.45	0.47
G 1	H.S.	0.0	0.0	0.0	0.0	Tr.
	H.V.	0.0	0.0	0.0	0.0	Tr.
B 3	F.S.	0.40	0.40	0.40	0.47	0.52
G 1	H.S.	0.0	0.0	0.0	Tr.	+1.0
	H.V.	0.0	0.0	0.0	Tr.	+1.0
B 4	F.S.	0.40	0.40	0.40	0.50	0.65
G 1	H.S.	0.0	0.0	0.0	+1.0	+2.0
	H.V.	0.0	0.0	0.0	+1.0	+2.0
B 5	F.S.	0.42	0.42	0.45	0.52	
G 1	H.S.	0.0	0.0	Tr.	+1.0	
	H.V.	0.0	0.0	Tr.	+1.0	
B 10	F.S.	0.42	0.42	0.45	0.55	
G 1	H.S.	0.0	0.0	Tr.	2.0	
	H.V.	0.0	0.0	Tr.	1.0	

The first three observations were made on the blood of one donor, the last two on that of another donor. F.S. = fragility to saline dilutions; H.S. = hemolysis on shaking; H.V. = visible hemolysis.

In an attempt to secure good preservation in even smaller volume 10.8%, 50%, and crystalline glucose were added to blood in different amounts in 7 experiments. Crystalline glucose produced some hemolysis at once, 50% glucose at the end of 7 days. The 10.8% glucose delayed hemolysis until the 28th day in one experiment, the 21st in another. With it, however, red cells swelled more, and plasma chloride decreased more sharply than with 5.4% glucose. Because of these observations isotonic glucose only was regarded as suitable for blood preservation.

Three observations were made with citrate-glucose-saline mixture, one with twice isotonic fluid (glucose 5.4%, saline 0.9%) and two with isotonic fluid. Hemolysis appeared on the 21st day in the first instance, on the 14th day in the other two.

Two observations only were made on the effect of anerobic storage, in both of which hemolysis appeared 7 days earlier than in controls.

This is contrary to the findings of De Gowin[3] and others. However, the technical difficulties involved in producing anerobic conditions and our satisfactory results under ærobic conditions removed our interest from further pursuit of this possibility.

TABLE 2.—THE COMPARATIVE KEEPING QUALITIES OF A SPECIMEN OF HUMAN BLOOD IN CITRATE, 0.4%, AND IN CITRATE-GLUCOSE AT 4° TO 6° C.

	Citrated Blood.								Citrated Blood, 2 Parts; Glucose 5.4%, 1 Part.									
Day:	0	1	2	3	4	6	7	14	0	1	2	3	4	6	7	14	21	28
Granulocytes	30	28	28	26	18	14	10	?	21	20	20	21	21	19	16	4	1	?
Platelets	145	115	92	86	56	43	49	28	96	92	89	82	69	59	63	46	40	23
Prothrombin time	12	12	13	13	14	14	15	18	17	17	17	17	18	16	18	22	25	31
Isoagglutinin	32	..	..	..	..	..	32	8	16	..	..	..	..	..	16	16	16	16
False agglutination	0	..	..	..	..	..	0	0	0	..	..	..	..	..	0	0	0	0
Hemoglobin	14	..	..	..	..	..	14	14	10.5	..	..	..	..	..	..	10	10	10
Oxygen capacity	16	..	..	..	..	..	16	17	12	..	..	..	..	..	13	14	13	13
Fragility NaCl	40	40	425	425	425	475	475	85	40	40	40	40	40	425	425	425	45	50
Hemolysis shaking	0	..	..	..	..	..	+2	+3	0	..	..	..	..	..	0	0	0	+1
Hemolysis visible	0	..	..	..	..	..	+1	+2	0	..	..	..	..	..	0	0	0	0
Hematocrit	39	..	..	..	..	..	40	40	33	..	..	..	..	..	33	34	33	34
Chloride plasma	578	..	..	..	..	..	570	572	392	..	..	..	..	..	..	390	..	368
Phosphate inorganic	4	..	..	..	..	..	7	10	3	..	..	..	..	..	..	3	..	5
Potassium	16	..	..	..	..	..	78	..	11	..	..	..	..	..	..	..	..	72
Glucose	85	..	..	..	..	..	20	18	1820	..	..	..	..	..	1810	1700	1590	1560
CO_2 plasma	47	..	..	..	..	..	21	14	37	..	..	..	..	..	11	1	1	?
Suspensibility	G	..	..	..	..	..	G	G	G	..	..	..	..	..	G	G	G	G
Culture	S	..	..	..	..	..	S	S	S	..	..	..	..	..	S	S	S	S

Granulocytes in hundreds; platelets in thousands per c.mm.; prothrombin time in seconds; isoagglutinin in dilution titer; hemoglobin in gm. per 100 cc.; oxygen capacity in vols. %; fragility NaCl in salt concentrations (40 = 0.4%); hematocrit as % of packed red blood cells; plasma chloride, inorganic phosphate, potassium, glucose, in mg. per 100 cc.; CO_2 plasma as vols. %; G = good, S = sterile. Fractions omitted.

The majority of those using glucose advocate bleeding donors directly into a citrate-glucose mixture. This has two disadvantages: first, glucose is apt to caramelize when sterilized with citrate; second, when a measured amount of preservative is placed in the reception flask prior to bleeding the proportions of blood and glucose will not always be the same because of the occasional failure to secure the amount of blood desired. For these reasons we prefer to add glucose after the blood has been collected. This is done by pouring in half as much glucose as blood, using the graduations on the bottle to measure by. The fluids are then mixed gently with a sterile glass rod. Quantitative determinations of top, middle and bottom portions of the fluid in six instances showed diffusion of glucose to be uniform throughout.

A second consideration connected with the practice of adding glucose after bleeding was the possible effect of delay in so doing. This was observed on a single blood divided into 5 equal parts. To 1 of these glucose was added at once and to the others after intervals of 6, 12, 24 and 48 hours. Hemolysis (shaking) appeared on the 20th day in the first 3 samples, in 5 days in the latter 2. We have assumed, consequently, that a 12-hour delay in adding glucose

in the case of an occasional specimen collected out of usual hours is permissible, though not ideal.

The ease with which blood and glucose might become infected has been studied by cultures of 100 specimens collected in routine fashion. All have been sterile.

Table 2 gives in detail a final comparative study of equal parts of blood from one donor received into 20% citrate to make a final concentration of 0.4%. To one part a half portion of 5.4% glucose was added. The only departure from the storage technique described above was that samples for the observations on the 2d to the 6th day inclusive were placed in test tubes.

Although the chief interest in this and similar studies has been the preservation of erythrocytes, from the standpoint of practical transfusion alterations in other elements of whole blood are of comparable importance. These studies were designed to include as many observations as practically possible, omitting, however, consideration of the antibacterial and immunological properties, which have been studied by Kolmer,[4a,b] and possible alterations of plasma.[5] In drawing conclusions use is made of chemical data, observations on white cells, platelets, and so on, similar to those in Table 2, but omitted for brevity. Such studies formed a part of all of 20 experiments on the various conditions of blood storage discussed above.

Loss of granular cells, platelets and prothrombin takes place perhaps a little more slowly in glucose, though the difference is slight when other of our experiments are examined. Howell's prothrombin time was done in 6 studies with varying amounts of 5.4% glucose and was found to increase only a little less rapidly than in citrate studies.[2] This depreciation in elements essential for the formation of clot seems sufficiently rapid to contraindicate the use of stored blood, even with glucose, in any of the hemorrhagic diathesis. The effect of granulocyte loss on transfusion in sepsis has been commented on by Kolmer. Isoagglutinins and isoagglutinogens were studied to be sure that storage would not interfere with accurate typing and cross agglutination. In none of the 8 experiments was there any loss of specific agglutinability, nor the development of abnormal agglutinating tendencies. Agglutinin titre was preserved a little better in glucose.

Hemoglobin, red cell numbers (counted on each day of observation, but omitted from table) and oxygen capacity remained essentially unchanged under all conditions. The most clear cut effect of glucose was to delay the development of definite erythrocyte fragility as shown by saline dilutions, from about the 6th day in citrate to the 21st day or 28th day. Hemolysis on shaking appears an interval later in Table 2, but in other observations the two changes were approximately simultaneous. It should be noted that the test for hemolysis by inspection, that is after mixing the cells and plasma

and centrifuging, is less sensitive than by shaking; and that inspection of the supernatant plasma is even cruder. Consequently the appearance of hemolysis in any specimen of stored blood shows that it is unfit for use. The idea that a little hemolysis makes no difference must be abandoned along with the concept that it is hemolyzed blood itself which is objectionable. Hemolyzed blood, certainly in moderate amounts, is harmless on intravenous injection. The importance of erythrocytolysis in stored blood is the indication it furnishes that the cells have already undergone such changes as to render them incapable of physiological function.

Other evidences of red cell changes are furnished. The hematocrit readings in Table 2 show no alteration in cell size. In other observations, however, especially in hypertonic solutions of glucose, swelling took place, and in general an increase in size of stored erythrocytes appeared to be correlated with hemolysis. Roughly parallel to cell swelling is decrease in plasma chloride, which, it appears, enters the cells. The loss in some instances was as great as 80 to 90 mg. per 100 cc. in 28 days. A shift of ions in the opposite direction is illustrated by the increase in inorganic phosphates and of potassium in the plasma. The retardation of the shift of ions by glucose is well shown. De Gowin and Scudder,[9] however, found potassium to diffuse at about the same rate in glucose as in citrate solution, in both being rather more rapid during the first period of storage than later. Glycolysis and a fall in carbon dioxide combining power is more rapid in bloods to which glucose has been added. This apparent inconsistency may be explained on the supposition that a slight change in the direction of acidity would delay hemolysis. These chemical changes have been discussed by Peters[7] and by Maizels and Whitaker.[6a,b]

These several evidences of alteration in the cellular element and in the clot promoting properties of stored blood were consistently present, and progressed steadily, differing only in that their development was less rapid under the more favorable conditions. Similar observations have been made by others, all of whom are in substantial agreement.

It is of some importance to note a difference in the keeping properties of blood from different donors under identical conditions. This, of course, has been a common observation with chilled citrated blood. It might be attributed to technical errors, such as too vigorous shaking, delay in chilling, and so on. In these experiments, however, technical details were carefully controlled, and so we are inclined to assign as the major cause of such differences variations inherent in the blood of different individuals. In any case this shows the wisdom of allowing a generous margin of safety in setting an upper age limit for stored blood. To us, 14 days seems reasonable, although in our best experiments no hemolysis was apparent at the 21st day. In support of this it was recalled that Rous and

Turner found rabbit erythrocytes physiologically active up to the 14th day, not so on the 21st, although hemolysis had not occurred.

Conclusions. Glucose (5.4%) prevents the hemolysis of erythrocytes of whole citrated human blood kept at 4° to 6° C., for 3 to 4 weeks. With citrate alone hemolysis appears near the end of the 1st week.

This preserving effect is less marked on granulocytes, platelets and on the clot-forming properties.

One part of isotonic glucose to two parts of blood is effective, and has the advantage of not increasing too greatly the amount of fluid to be injected.

It must not be thought that blood preserved by chilling and the addition of glucose remains in a state of hibernation, or suspended animation. The processes of decay go on steadily, being only retarded by the favorable environment. There is, therefore, a strict limit to the time that blood for transfusion may properly be stored. This limit is shorter than generally supposed because of the fact that these red blood cells become incapable of substituting for the cells of the recipient prior to suffering any hemolysis.

REFERENCES.

(1.) **Belk, W. P.**, and **Barnes, B. C.**: Am. J. Med. Sci., **201**, 838, 1941. (2.) **Belk, W. P.**, **Henry, N.**, and **Rosenstein, F.**: Ibid., **198**, 631, 1939. (3.) **De Gowin, E. L.**, **Harris, J. E.**, and **Plass, E. D.**: J. Am. Med. Assn., **114**, 850, 1940. (4.) **Kolmer, J. A.**: (*a*) Am. J. Med. Sci., **197**, 442, 1939; (*b*) Ibid., **200**, 311, 1940. (5.) **Lipp, W. F.**, and **Hubbard, R. S.**: Proc. Soc. Exp. Biol. and Med., **43**, 265, 1940. (6.) **Maizels, M.**, and **Whitaker, N.**: (*a*) Lancet, **1**, 113, 1940; (*b*) Ibid., p. 590. (7.) **Peters, J. P.**: Harvey Lectures, **33**, 112, 1937–38. (8.) **Rous, P.**, and **Turner, J. R.**: (*a*) J. Exp. Med., **23**, 219, 1916; (*b*) Ibid., p. 239. (9.) **Scudder, J.**, **Drew, C. R.**, **Corcoran, D. R.**, and **Bull, D. C.**: J. Am. Med. Assn., **112**, 2263, 1939. (10.) **Van Slyke, D. D.**, and **Stadie, W. C.**: in Practical Physiological Chemistry, by Hawk and Bergeim, Philadelphia, P. Blakiston's Sons & Co., Inc., 1937.

LEUKEMOID REACTIONS.

By J. M. Hill, M.D.,

associate professor of pathology; director of hospital laboratories, baylor university college of medicine, dallas, texas,

and

C. N. Duncan, M.D.,*

instructor in medicine, boston university college of medicine, boston, mass.

(From the Department of Pathology, Hospital Laboratory Division, Baylor University College of Medicine.)

Blood pictures simulating leukemia have been recognized as unusual reactions in rare non-leukemic conditions for several years. Since the introduction of chemotherapeutic agents of the sulfanilamide group, however, leukemoid reactions of varying grades of severity have become sufficiently common to arouse general interest

* Formerly Resident Pathologist, Baylor University Hospital, Dallas, Texas.

in the differential diagnosis of all conditions giving this type of blood picture.

The leukemoid reactions which result from therapeutic measures are more of a puzzle in confusing the prognostic interpretation of the differential count than as a diagnostic problem. However, a large number of other clinical conditions simulating leukemia may present great difficulties in diagnosis. Most numerous and diverse are the group of disease states which are capable of producing a myeloid type of reaction in the blood. We have found it particularly helpful in this type of blood picture to employ a classification based on causative mechanisms, evolved as a result of the study of many such cases at Baylor Hospital, involving as they did a heterogenous and widely diverse group of diseases and clinical conditions.

This classification has been of help, first of all, in suggesting the many abnormalities other than leukemia which must be considered with wide deviations of the blood picture from normal. In addition, diagnosis and differentiation from leukemia has been simplified due to the systematic arrangement of leukemoid reactions according to apparent causal mechanisms.

A rather voluminous literature concerning the probable causes of leukemoid blood pictures has accumulated, but relatively little has been attempted in classification. Krumbhaar[10] first applied the term "leukemoid" to blood pictures simulating leukemia and divided these reactions into the main groups, namely: (1) those presenting a real difficulty in diagnosis from leukemia and (2) those having hematologic similarity alone. Later Fitz-Hugh[6] classified these leukemia-like conditions according to their blood picture into myeloid, lymphatic, and monocytic types. He also commented on the difficulty of defining these groups of reactions, since leukemia itself exhibits such a variety of manifestations, even including a low count. Schilling[16] included direct bone marrow irritations as well as the non-leukemic myeloses under the heading of liberating leukocytoses, thus making no effort to separate these conditions on an etiologic basis.

In order to restrict the type of conditions under consideration here to those which actually simulate leukemia closely enough to be a diagnostic problem, we have adopted an arbitrary definition of the leukemoid picture in the selection of cases for this report. We considered as leukemoid any reactions in which the following were found: (*a*) Total leukocyte count over 50,000; (*b*) presence of immature cells of the "blast" stage; or (*c*) a combination of both (*a*) and (*b*).

The cause of leukemoid reactions has not been satisfactorily explained, although many conditions have been named which at times may result in such reactions, but which usually do not. For example, Heck[7] collected from the literature 16 clinical conditions which have been responsible for this type of blood picture.

CLASSIFICATION OF LEUKEMOID REACTIONS OF MYELOID TYPE ACCORDING TO APPARENT CAUSATIVE MECHANISM.

I. *Bone marrow irritation or stimulation:* This may be physical, chemical, or allergic in character.
   A. General features of blood picture.
      1. High leukocyte count, often over 75,000.
      2. Eosinophilia and basophilia frequently prominent.
      3. Degree of leukocyte immaturity less marked than in II and III, usual myelocytes with few or no myeloblasts.
   B. Conditions or diseases capable of producing this type of reaction.
      1. Osteomyelitis and complicated bone fractures.
      2. Metastatic carcinoma of bones.
      3. Chronic infectious granulomata of bone.
      4. Hodgkin's disease with bone marrow lesions.
      5. Severe reactions to intravenous medication.
      6. Severe reactions following transfusions.
      7. Pyogenic infections.

II. *Liberation leukocytosis:* Marrow response to overwhelming demand.
   A. General features of blood picture.
      1. Leukocyte count variable, usually less than in Group I.
      2. No definite eosinophilia in most cases.
      3. Degree of leukocyte immaturity generally greater than Group I.
   B. Conditions or diseases capable of producing this type of reaction.
      1. Acute hemolysis in:
         a. Sulfanilamide therapy (and related drugs).
         b. Familial hemolytic anemia.
         c. Blackwater fever of malaria.
         d. Sickle cell anemia.
         e. Hemolytic poisons, phenylhydrazine, and so forth.
      2. Erythroblastic anemia.
      3. Pernicious anemia in crisis.
      4. Following severe hemorrhage.
      5. Recovery phase of granulocytopenia.
      6. Polycythemia, especially in anemic phase such as following therapy.
      7. Septicemia.
      8. Stage of impending death in acute infections.

III. *Ectopic hematopoiesis:* Formation of blood producing foci outside of bones usually due to destruction or crowding of bone marrow.
   A. General features of blood picture.
      1. Leukocyte count relatively lower, often in normal range.
      2. Eosinophilia not prominent.
      3. Degree of leukocyte immaturity more marked than in Groups I and II.
   B. Conditions or diseases capable of producing this type of reaction.
      1. Osteosclerosis and osteofibrosis.
      2. Prolonged increased demand in:
         a. Chronic form of familial hemolytic anemia.
         b. Prolonged untreated pernicious anemia.
      3. Tumors with extensive replacement of bone marrow.
      4. Lipoid histiocytosis.

Tuberculosis has been most frequently given as a cause of leukemoid pictures, as the reports of Marzullo and deVeer,[13] Leibowitz,[12] Custer and Crocker[3] and others indicate. The relation of true

leukemia and tuberculosis has been a cause of confusion. Undoubtedly leukemia may cause breakdown and activation of tuberculous lesions, but, on the other hand, tuberculosis may in rare cases tend to suppress leukemic findings in the blood as Jaffe's[9] cases clearly demonstrate. Most illuminating is the work of Stasney and Feldman,[17] which showed a leukemoid reaction upon administration of tuberculin to previously sensitized animals.

Septic infections may simulate leukemia, either as an extremely active response of the marrow or more particularly, when the infection is directly in the marrow, as pointed out by Schilling.[16] Arneth[2] suggests a selective septic effect on one type of cell as the causative mechanism in pyogenic infections.

Carcinoma has frequently been reported as causing a leukemoid picture. Ercklentz,[4] and Kugelmeier[11] believe a toxic factor in carcinoma acts on the marrow. Muller and Werthemann[14] liken the tumor products to a parenteral injection of protein producing leukocytosis. Reich[15] assumes that a direct irritation due to metastatic carcinoma produces hyperplasia and leukocytosis.

Atypical blood pictures with osteosclerosis have frequently been confused with aleukemic myeloid leukemias because of the low count, and the extramedullary foci of hematopoiesis found in various organs. Anagnostu[1] points out that these reactions are compensatory responses to mechanical displacement of bone marrow. Stephens and Bredeck[18] also point out the primary rôle of the bone changes and the relationship of their severity to the blood picture. A similar displacement mechanism may be seen in the case of Niemann-Pick's disease described by Fisher.[5]

Many other conditions, apparently unrelated to each other have been reported as giving leukemoid reactions in rare or solitary cases. We believe, however, that most of these can be classified in respect to the mechanism by which blood formation is disturbed and the leukemoid blood picture produced.

Differentiation From Leukemia. The actual diagnosis and differentiation of any given case from true leukemia may be very difficult, but several practical points can be used. First, recognition of any of the clinical conditions capable of producing a leukemoid reaction should throw doubt on the additional diagnosis of true leukemia on the basis of a suggestive blood picture only. Of course, it must be understood that even the conditions listed need not produce a leukemoid picture constantly. In fact, in most of these leukemoid reactions are very much the exception. Second, useful differential features, and often definite criteria, can be made out by the hematologist in study of the blood smear. Finally, the finding from simple laboratory tests such as platelet count and hemoglobin may be helpful. The laboratory differentiation can be given in tabular form.

Leukemoid Picture.	*True Leukemia.*
1. Immature as well as mature leukocytes show normal morphology.	1. Leukocytes are atypical, particularly the immature ones.
2. Myeloblasts may be present but usually are under 10%.	2. Myeloblasts may be numerous, as high as 99+%.
3. Immature red cells (normoblasts and erythroblasts) often increased in proportion to leukocyte immaturity.	3. Immature red cells rarely increased in proportion to leukocyte immaturity.
4. Platelets usually normal or increased, may be moderately decreased in Group 3.	4. Platelets decreased, often severely, may be increased in chronic myelogenous form only.
5. Anemia variable depending on causal factors.	5. Steadily progressing anemia becoming extreme.

Our largest group of cases were those classified as bone marrow irritations. Of course, not all of these cases were completely clear cut, particularly in carcinoma with marrow metastasis where some marrow destruction and ectopic blood formation are seen as is illustrated in our first case. Case 2 is representative of osteomyelitis with marrow irritation. Typical of Hodgkin's disease with bone marrow lesions, Case 3 very closely simulates leukemia in its clinical picture, but is easily differentiated by biopsy. Case 4, remarkable for its exceedingly high count, apparently can be explained as a pyogenic infection with a selective septic irritating effect on marrow cells.

Case 1.—R. L. P., white female, aged 51, admitted with complaints of shortness of breath and blue spots on legs and arms for 2 weeks prior to admission. *Past history:* small mass in left breast, 1 year without apparent increase in size, loss of 95 pounds in 7 months.

Physical examination shows subcutaneous hemorrhages over legs, hips, and arms; heart slightly enlarged to left, rate rapid, rhythm regular; liver 4 fingers below costal margin. A small mass in left breast unattached to skin, size of walnut, was found.

Laboratory examinations: leukocytosis, fairly severe anemia, no definite depression of platelets and definite immaturity of leukocytes.

July 18, 1940. Red count, 2,520,000; leukocytes, 25,500; differential: 1 eosinophil, 1 basophil, 6 myeloblasts, 16 myelocytes, 18 young forms, 40 band forms, 3 segmented forms, 13 lymphocytes, and 3 monocytes.

July 20, 1940. Platelets, 210,000; leukocytes, 35,000; with large number of myelocytes, myeloblasts and pre-myeloblasts; also many erythroblasts.

Postmortem diagnosis: carcinoma of breast with tumor thrombi and hemorrhages, in breast, bone marrow, lung, liver, spleen and suprarenal. Small ectopic foci of hematopoiesis in liver, spleen and lymph node.

Case 2.—J. S., negro male, aged 40, entered the hospital complaining of low back pains for 3 months, and pain and difficulty in using the lower extremities for 2 months. This patient had been seen previously in the antiluetic clinic as early as 3 years ago, and at that time the leukocyte count was 23,000, with a differential showing 87% neutrophils with 13% lymphocytes. Over this 3-year period he had had several blood examinations, the leukocyte count varying from 23,000 to 66,000 with differential count showing 2% to 3% myeloblasts, 15% to 20% myelocytes, 20% to 40% eosinophils, 2% to 4% basophils, 7% to 13% lymphocytes, the remainder being neutrophils. At the time of admission he presented the picture of a slightly undernourished, slightly emaciated negro male, with

skin and mucous membranes pale. The heart and lungs appear normal, the abdomen showed 3+ tenderness and voluntary rigidity of the lower portion. Liver, spleen and kidneys were not palpable. Rectal examination revealed a firm prostate of normal size.

Laboratory examinations: total white count of 78,400, with a differential reading: eosinophils, 18%; basophils, 5%; myelocytes, 20%; band forms, 0%; segmented forms, 25%; lymphocytes, 2%. Red cells, 2,800,000 with 4% hemoglobin. Wassermann, Kahn and Kline tests were negative. Stool examinations for parasites were also negative. Spinal fluid: Wassermann test was negative, colloidal gold curve was negative, cell count was 4. Roentgen ray examinations were negative except for an unexplained shadow in the region of the right hip.

Clinical course: the patient continued to complain of pain in his back, abdomen and right side. He ran a sustained temperature of 101° to 102°; pulse, 120 to 130. Patient rapidly became weaker and died on the 34th hospital day.

Autopsy: chronic suppurative osteomyelitis of the sacrum; extensive gangrenous necrotic abscesses of right thigh and right side of the pelvis; abscess of the posterior lobe of the right lung; extensive suppurative bronchopneumonia of the posterior portion of the right and left lungs.

Case 3.—J. F., white male, aged 23, entered the hospital complaining of general malaise, fever, slight cough, and enlargement of the glands of the neck and groin for 4 months.

Physical examination revealed a rather well-developed but slightly undernourished and anemic-looking white male, not acutely ill. The neck showed extreme enlargement of the anterior and posterior cervical lymph glands and supraclavicular glands. These lymph nodes were discrete and movable but not tender. A similar type of glandular enlargement was noted in the axillæ and inguinal regions. The heart and lungs appeared normal and the spleen was palpable.

Laboratory examinations: red blood count 3,160,000 with 70% hemoglobin. White blood count 54,350 with the differential showing basophils 2, eosinophils 32, lymphocytes 10, neutrophils 55. Platelet count was 201,600. Wassermann test was negative. White blood count ran from 45,500 to 62,000 with 54 to 55 neutrophils, 25 to 31 eosinophils, 5 to 20 lymphocytes. Later admission to the hospital showed the lymph glands to be slightly larger. The patient also developed a rather severe diarrhea 6 months after the first admission. At this time the laboratory work showed a platelet count of 54,000. Red count 3,500,000 with 55% hemoglobin. White blood cells 50,250 with 48 eosinophils, 43 neutrophils, 4 lymphocytes, and 5 degenerative or unidentified cells. Reticulocytes, 1.2%. On one occasion at this time a few myelocytes were also seen. The patient became progressively worse and expired.

Autopsy: marked generalized Hodgkin's disease of lungs, liver, spleen, lymph glands and adrenals with numerous Hodgkin's lesions in the bone marrow.

Case 4.—M. M., a colored female, aged 24, entered the hospital in a comatose condition. Her chief complaints were a painful rectum and sore mouth for 3 days. On physical examination a draining ischio-rectal fossa abscess was found. Patient was acutely ill with temperature 102°, pulse 125, and respiration 29.

Laboratory examinations: initial blood count of 206,000 with a differential showing basophils 5, young forms 27, band forms 20, segmented forms, 38, lymphocytes 10. Later counts varied from 168,750 to 25,000 and showed a differential with from 1% to 2% myeloblasts, 7% to 13% myelocytes. Seven days from admission the count was 10,000 with a normal differential and remained so until time of dismissal.

Although the liberation leukocytoses do not constitute the largest groups in our series, it is probable that the most common leukemoid picture seen today will belong in this group. Case 5 of this group, with hemolytic anemia from sulfanilamide, is typical of this reaction. Cases 6 and 7 closely resemble each other with a mixture of young cells of lymphatic and granular types. In these 2 cases the myeloid response of the pyogenic infection seems to be heightened in some peculiar way by the earlier pertussis with its lymphocytosis. Also, the height of the leukocyte count is due in large measure to the absolute increase of lymphocytes. In familial hemolytic anemia, the blood picture may be hematologically identical to that induced by sulfanilamide and its related compounds. No case of hemolytic anemia is included here since in studying this disease, none of our series met the criteria set up in this paper. However, 1 case was seen with a high proportion of myelocytes and a leukocyte count of 40,000.

Case 5.—G. V. S., white female, aged about 30, was admitted to the hospital by way of the emergency room. She had been in a severe automobile accident, and was unconscious. An examination at that time revealed a fracture of the basal portion of the skull, a fracture of the right femur and numerous bruises and lacerations over the entire body. Her condition was very critical and she remained essentially the same until the 8th hospital day, at which time she developed a streptococcic meningitis. Sulfanilamide (120 grains) was given intravenously for 3 days and later, sulfanilamide (15 grains) was given orally every 4 hours, and then in decreasing doses.

Laboratory examinations: on admission the white count was 16,300 with a left shift present. Red count was 3,420,000 and hemoglobin 71%. After the development of meningitis and the first dose of sulfanilamide, the total white count was 53,700 with the differential showing 3 myelocytes, 2 young forms, 26 band forms, 50 segmented forms, 17 lymphocytes, 2 monocytes, 5 erythroblasts and 23 normoblasts, per 100 white cells. Sulfanilamide was discontinued on the 19th hospital day and 5 days later the blood smear showed a total white count of 9500 with no abnormal cells present in the blood smears examined. At the time the intravenous sulfanilamide was given, her sulfanilamide concentration was 9.4 mg. per 100 cc. This concentration varied from 7 to 30 mg. per 100 cc. over the 11-day period, during which she was receiving the drug. During this time the red cells dropped to 2,450,000 and numerous small repeated blood transfusions were given. The reticulocyte count showed a 12% response.

The patient improved and was discharged after a lengthy stay in the hospital. Later blood smears showed no abnormal cells.

Case 6.—D. H., aged 2½ years, was admitted to the hospital with a clinical diagnosis of whooping cough. During the course of his stay the child later developed lobar pneumonia. The total white count at that time was 52,875; differential: 1 myelocyte, 16 young forms, 24 band forms, 9 segmented forms, 43 lymphocytes, 6 monocytes, and 1 lymphoblast. Two nucleated red cells were also seen per 100 white cells examined.

The patient improved and was discharged at a later date. No abnormal cells were found at other examinations.

Case 7.—This case is similar to Case 5. A 5-year-old child was admitted to the hospital with a clinical case of empyema following an attack of pneumonia. At that time the white count was 103,000 with a severe left

shift present. Many myelocytes and about 50% lymphocytes were found on the differential count.

The patient improved and the count returned to normal at the time of discharge.

The most interesting group of our classification is made up of those leukemoid reactions associated with ectopic blood formation. This is apparently due either to actual physical reduction of bone marrow volume below the amount necessary to maintain normal blood cell values or to a chronic excessive demand which the normal marrow is incapable of supplying alone. Case 8 illustrates the first mechanism, Case 9 the second.

CASE 8.—B. H., a colored female, aged 46, entered the hospital complaining of weakness, swelling of the abdomen, dyspnea, dependent edema and loss of weight for 8 months. The present illness had an insidious onset with the symptoms gradually progressing and increasing in intensity to the time of admission.

Physical examination revealed an emaciated colored female, markedly dyspneic and orthopneic, appearing acutely ill. The skin and mucous membranes were markedly pale, the chest showed moist râles along both bases of the lung. The heart was enlarged to the left. Apex impulse in the sixth interspace 3 inches from the midline. The liver was enlarged, being palpated 10 cm. below the costal margin in the midclavicular line. The spleen was also palpable and enlarged and abdominal fluid was demonstrable. The vaginal examination revealed a nodular enlarged uterus which was also palpated from the exterior. Dependent pitting edema of the extremities was seen.

Laboratory examinations showed the Kline test to be 4+, red blood count 1,720,000, with 17% hemoglobin. White count was 10,500 with a differential showing 2 basophils, 16 band forms, 8 young forms, 27 segmented forms, 8 lymphocytes, 6 myelocytes, 2 micromyeloblasts, 27 myeloblasts, 1 erythroblast, and 1 normoblast. Platelet count was 101,000. A sternal puncture was attempted, but the operator experienced great difficulty in obtaining a specimen. In fact, it is stated that no actual marrow was obtained, and a differential count made on the fluid obtained at the sternal puncture revealed essentially the same as that of a blood smear. The patient's condition was very critical and she expired on the second hospital day.

Autopsy: osteosclerosis with ectopic hematopoiesis of the lungs, liver, spleen, kidney and lymph glands.

CASE 9.—J. B. A., white male, aged 60, was known to have been always somewhat pale, and to have had splenomegaly at 10 or 12, and at 25 years of age. Since the age of 25, he has had intermittent attacks of splenomegaly, usually lasting a month or so with associated loss of 10 to 20 pounds. During these times there have been no particular symptoms other than awareness of splenic tumor and some slight tenderness in the RUQ. Since 1933 the patient has been treated occasionally by Roentgen ray therapy. During the past 10 years attacks have been more frequent and severe and of longer duration. Record shows 2 attacks of jaundice in youth.

Gastro-intestinal complaints, particularly pertaining to gaseous indigestion, have been voiced for many years. In addition, the following complaints are listed, which have no direct connection with the illness as stated above: habitual constipation; pyorrhea, necessitating removal of all teeth; appendectomy at about 30; repair of postoperative hernia at 50, with release of an adhesion near the spleen at that time; rheumatic pains in elbows, knees, and calves of legs, increasingly worse; visual complaints for a period of many years, apparently with no correlated organic finding.

The electrocardiogram shows frequent ventricular premature contractions; left axis deviation, otherwise negative.

Laboratory examinations: red blood count, 4,500,000; icterus index, 10; reticulocytes, 11%. The fragility was increased but occasionally approached normal. The red corpuscles were of small diameter and thicker than normal. Leukocytes ranged from normal to 15,000 per c.mm.; in one hemolytic episode they were as high as 73,500. There were some immature leukocytes at all times, but they became very numerous when the leukocyte count was high. Even when the counts were within the normal range myelocytes and myeloblasts were constantly present. The differential count in the worst episode with the leukocyte count, 73,500, was as follows: 2 basophils, 1 eosinophil, 5 myeloblasts, 9 myelocytes, 34 young forms, 40 band forms, 4 segmented forms, 5 lymphocytes. At all times the immature leukocytes were perfectly regular and typical in every respect. Usually a variable number of immature red cells were present, including normoblasts, erythroblasts and rare megaloblasts.

Discussion. The cases reported in this paper illustrate the many varieties of disease states which may give leukemoid reactions. They also indicate wide differences in the ease or difficulty of diagnosis as represented by the reaction of sulfanilamide and the unusual case of osteosclerosis. Despite the very close similarity of some of these blood pictures to leukemia, we believe it is essential to recognize the fundamental dissimilarity of the basic pathologic changes. In leukemia there is an unrestrained proliferation of a primary nature of abnormal immature leukocytes in normal (bone marrow) and abnormal (other organs and tissues) locations. In leukemoid states there may be proliferations secondary to other causes of normal immature leukocytes in abnormal locations. These proliferations called ectopic hematopoiesis are limited, according to the need for such cells in the blood, and unlike the proliferations in leukemia do not overgrow and encroach upon normal tissues with serious impairment of organ function. Another point of difference is that all the myeloid elements are found in the ectopic foci of leukemoid reactions. Not only are myelocytes and myeloblasts found, but also erythroblasts and megakaryocytes.

The leukocyte count which is one of the chief points of similarity between leukemoid states and true leukemia is not one of the essential characteristics of leukemia. On the contrary, the count in leukemia may be lower than normal. The number of leukocytes in the blood seems to be related to the level of maturation of the immature cells proliferating in the tissues, as pointed out by one of us[8] in an earlier paper. Of course, leukemoid reactions may also show low counts, and in these cases we find the greatest immaturity of leukocytes and greatest difficulty in diagnosis. However, in the leukemoid case the immature cells are abnormal only in their lack of maturity. They do not show the atypical features of leukemic cells such as abnormal lobulation, indentations or clefts of nuclei, or unusual granulations such as Auer rods. Another important abnormality of leukemic cells which we have not seen in leukemoid

reactions is the lack of correlation between the apparent age of the nucleus and the age of the cytoplasm. Such morphologic differences in the cell are important to the hematologist and may in rare cases be the chief and distinguishing feature.

The most extreme example of leukocyte immaturity in our series was Case 8. In this case, due to virtual elimination of all bone marrow by sclerosis, ectopic foci carried on practically all the blood formation. To make things worse a large portion of this ectopic myeloid tissue in lymph nodes was destroyed by tuberculous lymphadenitis. The extreme demand apparently resulted in the proliferation and release of cells which we believe to be even more immature than myeloblasts, corresponding to the primitive free cell of Sabin.

While classification of leukemoid reactions according to their general mechanism of causation as herein proposed is easily done in most instances, it is difficult or impossible to determine the exact abnormalities of leukocyte proliferation, maturation or release responsible for the blood pictures of these cases. Under our first group of marrow irritation, little can be said concerning the stimulation of proliferation or maturation responsible for very high counts since the factors influencing these processes are not well understood. In some cases there seems to be an unusual response to substances produced in pyogenic infections, while in others there is some obscure relationship to the effect of location of lesions actually in the bone marrow.

Normally, the leukocyte release mechanism seems to depend on the fact that active motility is found only in the relatively mature cells. To get into the blood stream from their extravascular point of origin, these leukocytes pass through the endothelium of the marrow capillaries and sinuses by ameboid movement. In our first classification two possible factors may be assumed, the one very active proliferation, the other damage and even actual breaks in the vascular endothelium of the marrow. Could it be that this combination of growth pressures together with capillary and sinus damage permits the immature non-motile cells to be washed into the blood stream? That such damage to vessels may occur is demonstrated in Case 1, where tumor thrombi and hemorrhages were found in the bone marrow. With liberation pictures, the release of immature cells is even more obscure in its mode of operation. Here again, however, injury to the endothelium by toxins, anoxemia or chemical poisons may be a factor. In the case of ectopic hematopoiesis, normal control of leukocyte release is lost because of the abnormal location of blood cell formation. In these ectopic foci, such as in the spleen or liver, hematopoiesis is not necessarily extravascular and as a consequence, immature cells may easily be washed into the circulating blood.

Conclusions. 1. A classification of leukemoid reactions of myeloid type is presented.

2. Cases illustrating this classification are reported.

3. Differentiation of the leukemoid picture from leukemia is discussed.

REFERENCES.

(1.) **Anagnostu, J. L.**: Folia haemat., **50**, 70, 1933. (2.) **Arneth, J.**: Deutsch. Arch. f. klin. Med., **180**, 620, 1937. (3.) **Custer, R. P.**, and **Crocker, W. J.**: Folia haemat., **46**, 359, 1932. (4.) **Ercklentz, B. W.**: Ibid., **53**, 382, 1935. (5.) **Fisher, C. F.**: Arch. Pediat., **49**, 574, 1932. (6.) **Fitz-Hugh, T., Jr.**: Pennsylvania Med. J., **35**, 290, 1932. (7.) **Heck, F. J.**, and **Hall, B. E.**: J. Am. Med. Assn., **112**, 95, 1939. (8.) **Hill, J. M.**: Texas State J. Med., **32**, 352, 1936. (9.) **Jaffe, R. H.**: Am. Rev. Tuberc., **27**, 32, 1933. (10.) **Krumbhaar, E. B.**: Am. J. Med. Sci., **172**, 519, 1926. (11.) **Kugelmeier, L. M.**: Folia haemat., **53**, 370, 1935. (12.) **Leibowitz, S.**: Arch. Path., **25**, 365, 1938. (13.) **Marzullo, E. R.**, and **deVeer, J. A.**: Am. J. Med. Sci., **182**, 372, 1931. (14.) **Muller, A.**, and **Werthemann, A.**: Folia haemat., **46**, 429, 1932. (15.) **Reich, C.**: Am. J. Cancer, **26**, 781, 1936. (16.) **Schilling, V.**: The Blood Picture and Its Clinical Significance (transl. by R. B. H. Gradwohl), 7th and 8th rev. eds., St. Louis, C. V. Mosby Company, p. 168, 1929. (17.) **Stasney, J.**, and **Feldman, W. H.**: Am. J. Cancer, **34**, 240, 1938. (18.) **Stephens, D. J.**, and **Bredeck, J. F.**: Ann. Int. Med., **6**, 1087, 1933.

ATRIOVENTRICULAR NODAL RHYTHM.

By Nathan Flaxman M.D.,

CLINICAL ASSOCIATE IN MEDICINE, LOYOLA UNIVERSITY MEDICAL SCHOOL, ASSOCIATE ATTENDING PHYSICIAN, COOK COUNTY HOSPITAL, CHICAGO, ILL.

(From the Department of Medicine, Loyola University Medical School, and the Columbus Hospital.)

The extensive use of the electrocardiograph has served to emphasize the importance of abnormalities in the rate and rhythm of the heart. Such a cardiac disturbance requiring careful interpretation is atrioventricular nodal rhythm, in which the auriculoventricular node assumes the rhythmiticity of the heart independently of the sino-auricular node. Three conditions are necessary for the establishment, even for a short time, of atrioventricular rhythm: 1, marked depression of the normal pacemaker of the heart and failure of any other part of the auricular muscle to assume this rôle; 2, normal activity (potential or latent ordinarily) of the pacemaking function of the auriculoventricular node; and, 3, ability of the impulse to pass backward from the junctional tissue into the auricles to cause their contraction, that is, an absence of a state of reversed block.[13a] During the time that the A-V node is acting as pacemaker the auricles respond to impulses from below, the ventricles to impulses from above.[1]

In the literature to date 50 cases of nodal rhythm, due to a variety of causes, have been reported. It has been observed in apparently normal hearts,[14] following auricular flutter,[13b] due to atropine,[15] digitalis,[12] subacute bacterial endocarditis,[5] coronary thrombosis,[9,11] scarlet fever,[6] quinidine sulphate,[8] active rheumatic fever,[3] anesthesia,[10] sulphanilamide,[4] and essential hypertension.[7]

Clinically, certain cardiac features may be present but none are

distinctive of nodal rhythm. The heart rate may be normal (60 to 99), slow (30 to 59—nodal bradycardia), or rapid (100 to 160—nodal tachycardia). Marked palpitation may be a major complaint as a result of the simultaneous contraction of the auricles and ventricles.[15] Unduly large impulses in the jugular vein due to the synchronous contraction may also be present.[2]

The diagnosis of atrioventricular nodal rhythm, however, can be made with certainty only by means of the electrocardiogram. In the electrocardiogram it is indicated by the *P* wave, usually inverted, falling within or just after the *QRS* complex. The ventricular complex is normal in form. Even the electrocardiogram can and does offer some difficulty in interpretation due to the simultaneous presence of other changes in the tracing. Nodal rhythm may be confused with auricular fibrillation with complete heart block, especially if in the nodal rhythm the *P* wave is buried in the *QRS* complex and nodal bradycardia is present. Here the absence of jugular pulsation in fibrillation and the presence of unduly large jugular waves in nodal rhythm may be a helpful differential point.

TABLE 1.—DATA ON 12 CASES OF ATRIOVENTRICULAR NODAL RHYTHM.

Case.	Age.	Sex.	Heart disease.		Heart rate.	Nodal rhythm.		Cause of death.	Comment.
			Type.	Duration.		Cause.	Duration.		
1	42	M	Hypertensive	2 mos.	90	Hypertension	4 wks.	Uremia	
2	68	M	Hypertensive	5 yrs.	70	Hypertension	3 wks.	C.H.F.*	
3	56	M	Hypertensive	2 wks.	98	Cor. thrombosis	2 wks.	.....	Recovered
4	62	M	Hypertensive	1 yr.	100	Cor. thrombosis	1 wk.	Cor. thrombosis	
5	52	M	Hypertensive	6 mos.	150	Hypertension	2 wks.	.....	Recovered
6	47	M	Hypertensive	1 yr.	66	Hypertension	1 mo.	C.H.F.*	
7	65	F	Hypertensive	5 yrs.	50	Cor. thrombosis	1 wk.	.....	Recovered
8	20	F	Rheumatic	5 mos.	66	Rheum. activity	1 mo.	.....	Recovered
9	18	M	Rheumatic	11 yrs.	110	Rheum. activity	1 mo.	.....	Recovered
10	84	M	Coronary	10 yrs.	150	Cor. sclerosis	1 mo.	Bronchopneumonia	
11	28	M	Syphilitic	2 mos.	76	Syphilis	3 wks.	.....	Recovered
12	18	F	Thyrotoxic	8 mos.	150	Thyrotoxicosis	1 mo.	Postop. myoc. failure	

* Congestive heart failure.

During the past 10 years I have seen 12 instances (0.6%) of atrioventricular rhythm among 2000 patients with organic heart disease from whom electrocardiograms were available. Nine were males and 3 females, a ratio of 3 to 1. As previously reported,[10,13b] it is an infrequent condition but one which may have important significance. It requires careful interpretation during the course of acute infectious diseases, acute coronary artery thrombosis, or when the nodal rhythm becomes chronic. Among the 12 patients who had nodal rhythm the underlying heart disease was most commonly due to essential hypertension (58.3%), but in 3 of these 7 an acute coronary artery occlusion was the precipitating cause (Table 1).

Six patients (50%) had a normal rate, 5 (41.6%) had nodal tachy-

cardia, and 1 (8.4%) had a nodal bradycardia. Although it had no relation to the cause of death, 6 patients (50%) died while the nodal rhythm was present. The duration of the nodal rhythm among those who recovered was on the average approximately 3 weeks. Digitalis was not given unless it was indicated, and among those who received this drug for the symptoms and signs of cardiac decompensation, no effect was observed on the nodal rhythm. Quinidine sulphate was not given to patients with nodal tachycardia, as this drug tends to depress the auricular musculature and to prolong the duration of the abnormal conduction. No instances of reciprocal rhythm were noted in this series. This mechanism was first described by Drury[5] and later by Jones and White.[9] In it the auricular contraction following the nodal impulse is sufficiently delayed so that it gives rise to a second ventricular response causing bigeminy.

The 4 illustrated cases have been appended to indicate some of the interesting features of nodal rhythm.

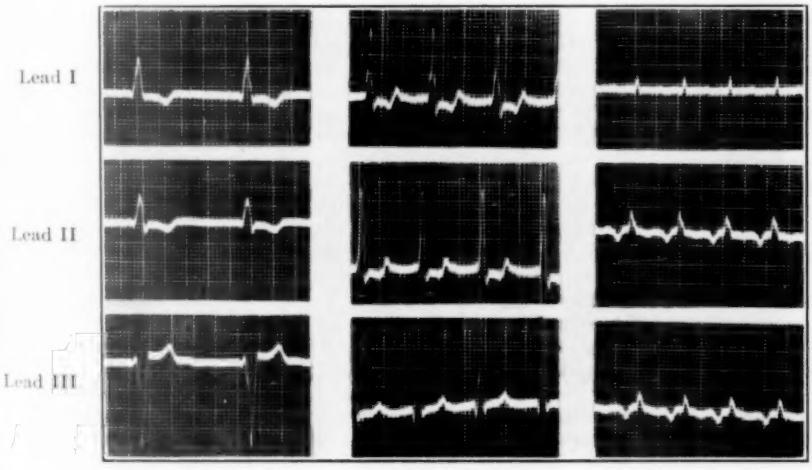


FIG. 1.—Electrocardiograms on Cases 6, 9 and 10.

Case Abstracts. CASE 6.—I. W., a 47-year-old white male, was a known hypertensive of 3 years' duration. At the age of 45 he had a cerebral hemorrhage with a resultant left hemiplegia. When first seen in December, 1937, he complained of increasing dyspnea of 3 months' duration. Physical examination revealed a blood pressure of 130/100, impaired resonance and moist râles at the bases of both lungs, a transverse cardiac diameter of 19 cm., a regular rate of 68 at the apex, the liver 4 cm. below the costal margin and tender, and moderate edema of the ankles. An electrocardiogram (Fig. 1), before digitalis was given, showed a rate of 66, marked left axis deviation, no *P* waves, and *T* waves inverted in Leads I and II. There was no response to digitalis and diuretics, and he continued to lose

ground steadily. A second electrocardiogram, repeated after 3 weeks, still showed nodal rhythm, but one taken after a month showed normal rhythm and a bundle branch block. He continued downhill and expired 6½ months after the onset of cardiac symptoms. An autopsy revealed eccentric hypertrophy of the heart, which weighed 620 gm., mural thrombi in the apex of the left ventricle, thrombosis of the left innominate, subclavian, and internal jugular veins, marked passive congestion of the liver, spleen and kidneys, bilateral hydrothorax with compression atelectasis of the basal portions of the lobes, ascites, pitting edema of the lower extremities, and passive congestion and edema of the brain.

CASE 9.—S. P., an 18-year-old white male, was known to have "heart trouble" since he was 7. He complained of dyspnea and vomiting of 2 days' duration. Examination revealed the blood pressure of 158/60 and a transverse cardiac measurement of 19 cm. There was a systolic thrill at the base of the heart, and loud rumbling systolic-diastolic murmurs over the aortic and mitral areas. Both the Corrigan and Duroziez signs were present. The liver was not palpable and no edema was noted. The cardiac rate was 110 and regular. An electrocardiogram (Fig. 1) showed a rate of 110, no visible *P* waves, and *T* in Leads I and II biphasic with a low take-off. On absolute bed rest he responded readily to digitalis and salicylates, and was well again in 3 weeks. Another electrocardiogram still showed nodal rhythm, but a third, 4 weeks after the onset, showed the presence of bifid *P* waves. The final diagnosis was rheumatic myocarditis with aortic and mitral stenosis and insufficiency with nodal rhythm.

CASE 10.—W. T., an 84-year-old white male, was known to have arteriosclerotic (coronary) heart disease for at least 10 years. He had retired 14 years before at the age of 70 and lived a life of limited activity. Two months before his death he complained of precordial and epigastric pain, dyspnea, and cough which confined him to bed. Physical examination revealed moist râles at the bases of both lungs, no apparent cardiac enlargement, a regular tachycardia of 154 beats per minute, liver 5 cm. below the costal margin and tender, marked palpable peripheral arteriosclerosis, but no edema. The electrocardiogram (Fig. 1) showed a low voltage tracing with a rate of 120, negative *P* waves, and notching of the *QRS* complexes. He responded well to digitalis and became compensated in 3 weeks. The nodal tachycardia persisted. One week later he developed a confluent bronchopneumonia which caused his death within 48 hours.

CASE 7.—D. W., a 65-year-old white female, complained of dizziness of 2 weeks' duration when first seen in August, 1933. At that time physical examination revealed a blood pressure of 160/100, heart borders within normal limits, and generalized peripheral arteriosclerosis. During the next 10 months she had an occasional complaint of headache and dizziness and the blood pressure varied between 180/120 and 140/90. In June, 1934, she suddenly became short of breath and complained of marked palpitation. When seen within a few hours the blood pressure had dropped to 100/70, and an auricular fibrillation with a rate of 150 at the apex was noted. This responded readily to quinidine, the rhythm becoming regular and the rate dropping back to 60 after 21 grains of the drug were taken orally. She felt very well until the middle of September, 1934, when a paresis of the right side of the face and the left upper extremity appeared, but this disappeared in a week. She continued well for over a year, but then began to have other attacks of auricular fibrillation, and all responded to quinidine. Attacks of the rapid irregular irregularity occurred in November, 1935; in December, 1936; in April, 1937; and in July, 1938. An electrocardiogram (Fig. 2) was taken between attacks on February 12, 1937. All 5 attacks of fibrillation occurred between midnight and 6 A.M.

On April 20, 1939, after an apparently uneventful 9 months, she collapsed

while preparing the evening meal at 5 P.M. When seen within ½ hour she appeared to be in deep shock. No pulse was felt at the wrist and the heart tones were barely audible. She was removed to the hospital by ambulance after morphine was given for the restlessness. There, oxygen was administered by nasal catheters, and at midnight, after a lapse of 6½ hours, the pulse became palpable at the wrist.* The rate was 50 per minute. Because of the slow rate and the severity of the attack it was thought that she had a coronary occlusion with auricular fibrillation and complete heart block. An electrocardiogram, taken the next day (Fig. 2), when her condition was poor, showed a rate of 50 per minute, no *P* waves, and regularly spaced *QRS* complexes. This tracing also suggested complete

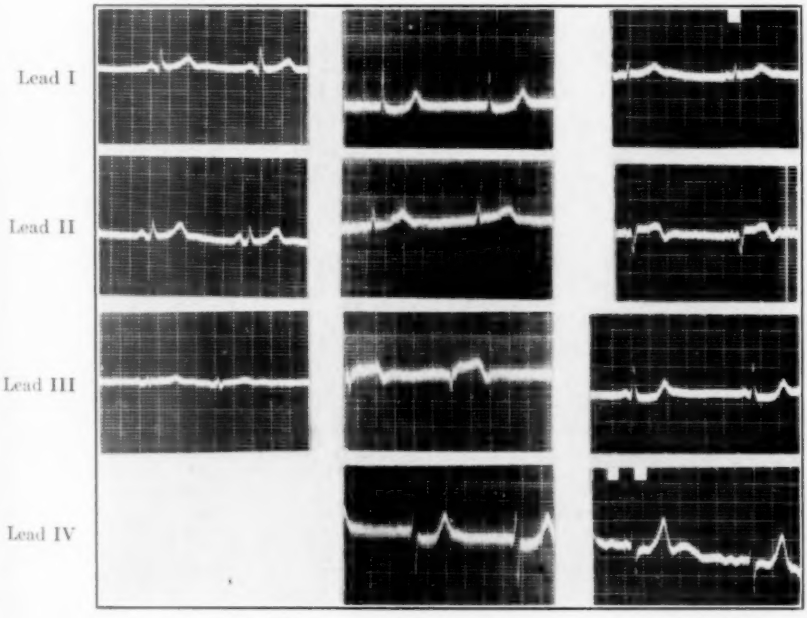


FIG. 2.—Electrocardiograms on Case 7.

heart block and auricular fibrillation, but the clinical findings indicated otherwise as she improved. The jugular pulsations were unusually large, regular, and counted at a rate of 50, and the same rate was noted over the cardiac area and at the wrist. Nodal bradycardia seemed to be more

* Robert Adams (1791–1875), a surgeon who made important contributions on cardiac subjects, noted first the sudden cessation of the pulse in a case which he considered an irregular form of angina pectoris and after an autopsy stated, "The organic seat of the gentleman's complaint was to be found in an ossified condition of the coronary arteries and aortic valves." In commenting on this (Ann. Med. Hist., 1, 3d ser., 49, 1939), Dr. James B. Herrick said, "Some may question the fact that a patient with acute coronary occlusion can live for days with no perceptible peripheral pulse. I am sure, however, that this is possible. I saw one case in which no radial pulse could be felt for six or eight hours before death, the patient being quite conscious during this time. In another patient who lived for five weeks after a coronary accident there was never felt during this period more than a rapid, extremely small, thready radial pulse. For hours at a time neither nurse nor doctor could feel it at all."

likely. On April 22 her condition was much better and from then on she continued to improve during the 6-week stay in the hospital. The heart size increased from 11 cm. before the occlusion to 18 cm. after the coronary accident, and then gradually returned to the original size at the end of the 6 weeks in bed. No digitalis was given by any route at any time as there were no indications for its use. An electrocardiogram on April 25 still showed a nodal bradycardia, but one on the 28th (Fig. 2) revealed a rate of 60 and the presence of *P* waves. She returned home and remained well until October 11, 1939, when an attack of auricular fibrillation occurred again. The attacks recurred on January 19, 1940, on July 12 and September 8, and the last one to date on October 1, 1940. Since the coronary occlusion and nodal bradycardia the four attacks of fibrillation failed to respond to quinidine, but have responded to digitalis within 2 days. Also, these attacks all occurred at night. When last seen in April, 1941, she was active at home and in fair condition, complaining only of weakness.

Summary. Atrioventricular nodal rhythm is an infrequent cardiac conduction disturbance which can be diagnosed only with the aid of the electrocardiograph. Its importance rests chiefly on the two facts that it is due to a large variety of causes, both cardiac and extracardiac, and that it indicates depression of the normal pacemaker of the heart, the sino-auricular node.

Neither digitalis nor quinidine, nor any other special drug is indicated in treatment, since nodal rhythm does not tend to persist after the cause has subsided or has been removed. Treatment, if possible, should be directed against the underlying cause.

REFERENCES.

(1.) **Ashman, R.**, and **Hull, E.**: Essentials of Electrocardiography, New York, The Macmillan Company, p. 163, 1937. (2.) **Chamberlain, E. N.**: Lancet, **2**, 1383, 1927. (3.) **Cutts, F. B.**: Am. Heart J., **13**, 451, 1937. (4.) **Dozzi, D. L.**: Am. J. Med. Sci., **195**, 771, 1938. (5.) **Drury, A. N.**: Heart, **11**, 405, 1924. (6.) **Duchosal, P.**, and **Sciclounoff, F.**: Arch. des mal. du coeur, **27**, 409, 1934. (7.) **Flaxman, N.**: Arch. Int. Med., **65**, 595, 1940. (8.) **Hall, D.**: Lancet, **2**, 589, 1936. (9.) **Jones, T. D.**, and **White, P. D.**: Am. Heart J., **2**, 266, 1927. (10.) **Levine, S. A.**: Clinical Heart Disease, Philadelphia, W. B. Saunders Company, p. 361, 1937. (11.) **Master, A. M., Dack, S.**, and **Jaffe, H. L.**: Ann. Int. Med., **11**, 735, 1937. (12.) **Richardson, H. B.**: Arch. Int. Med., **29**, 253, 1922. (13.) **White, P. D.**: (*a*) Heart Disease, New York, The Macmillan Company, p. 684, 1934. (*b*) Arch. Int. Med., **16**, 517, 1915. (14.) **Willius, F. A.**: Clinical Electrocardiograms, Philadelphia, W. B. Saunders Company, p. 148, 1929. (15.) **Wilson, F. N.**: Arch. Int. Med., **16**, 989, 1915.

TIBIAL ARTERY CHANGES IN COMPARISON WITH THOSE OF THE RADIAL AND CORONARY ARTERIES.

By S. W. Sappington, M.D.,
PATHOLOGIST, HAHNEMANN HOSPITAL,
AND
J. Arthur Horneff, M.D.,
ASSISTANT PATHOLOGIST, HAHNEMANN HOSPITAL,
PHILADELPHIA, PA.

(From the Department of Pathology, Hahnemann Medical College.)

The observations in this study are supplementary to those reported previously in a paper on "Radial Artery Changes in Comparison with Those of the Coronary and Other Arteries."[13] In this

paper, age period changes and arteriosclerotic changes were studied comparatively in the radial and coronary arteries from the same patient in a series of 86 cases.

In the present investigation, 61 tibial arteries were studied and compared with the radial and coronary vessels from the same case as well as with each other, to contrast the differences at various age periods. The age distribution of the 61 cases was as follows: Up to 40 years, 11; fifth decade, 13; sixth decade, 14; seventh decade, 14; eighth decade and above, 9. There were 35 males and 26 females in the group. The 61 cases covered a variety of diseases, some of which might be expected to favor vascular change: others, which are considered to have no influence in that direction. The only cases which were purposely avoided were those presenting definite signs of arterial obstruction in the extremities, as the present object was to show the average changes, individually and comparatively, in vessels of the lower extremities, as represented by the tibial artery, in cases without definite peripheral vascular disease. Thus cases of arteriosclerosis obliterans and thrombo-angiitis obliterans were excluded. The study of occluding lesions in sclerotic arteries of the lower extremities is the subject of a separate paper now under way.

In contrast to particular studies of the radial artery,[7,8,13,15] systematic studies of the pathologic histology of the small muscular arteries of the lower extremities, as typified in the tibials, seem to be scanty. It is true that there are histologic descriptions of the arterial changes in gangrene[2,3,16] and roentgenologic studies of calcific changes in arteries of the lower extremities,[10,11] but investigations on age period changes and arteriosclerosis short of obstructive alterations leading to gangrene are difficult to find and seem to be confined to incidental allusions[4,9,12] or general statements.[1]

Method. In each case, sections were taken from the lower anterior tibial artery just before it passes over into the dorsalis pedis; from the radial artery at the wrist; and from the right and left circumflex and anterior descending branches of the coronary artery. These were stained with hematoxylin and eosin, and with Weigert's elastic stain and van Gieson. The studies of the tibial and radial arteries were exclusively microscopic as it is difficult to get permission for removal of these vessels at autopsy and only short sections could be taken.

Age Period and Sclerotic Changes in the Tibial Artery. In the large coronary arteries, changes with advancing age develop to a maximal degree, so marked as to make them available for meticulous analysis.[5,6,17] Here the almost exclusively intimal changes permit the recognition, from without inward, of the musculo-elastic, elastic-hyperplastic and innermost connective tissue layers, as well as disappearance of the border between the intimal and muscular layers and the appearance of an intermediary layer there. This is capped in the late decades by eccentric, intimal, atherosclerotic develop-

ments which tend to cut down or occlude the lumen. In the smaller radial artery, these intimal details, though described by Hesse,[8] are not as a rule discernible. Instead, there is noted the progressive splitting of the intimal elastica and the interweaving of an increasing amount of longitudinally arranged, connective tissue, forming finally and collectively a fairly uniform intimal collar gradually increasing in thickness. This thickening is relatively and actually very much less than that seen in the coronaries, and atherosclerotic changes so common in the coronaries are scarcely seen in the radials. On the other hand, medial calcification, absent in the coronaries, is frequently seen in the radial vessels.

Study of tibial artery sections in advancing decades shows, as would be expected, changes comparable with those seen in the radial artery rather than those of the coronary. A tibial artery from a stillborn showed a single layered internal elastica immediately beneath the endothelial covering. At 14 and 21 months, the tibial arteries exhibited slight splitting of this elastic layer. At 4 years, there was apparently a very slight thickening of the subendothelial layer and in an artery from a child of 5, there was slight but definite subendothelial thickening by connective tissue fibers between the split elastica. The next artery, however, from a child of 7, showed no changes, and even splitting was absent, though the corresponding coronary vessel exhibited slight atherosclerosis. At 9 years, the tibial artery presented slight subendothelial thickening. In the second decade, there was some exaggeration of these changes. But in the third decade, there was what might be termed moderate subendothelial hyperplasia with further elastic splitting. This was particularly well seen in a tibial artery from a patient of 25. And at 30, an artery showed a trace of calcification at the intimal-medial junction. An artery from a 37-year-old subject exhibited marked medial calcific sclerosis in addition to intimal changes, but this case was one of malignant hypertension and hardly a fair example of average age period changes. In the fifth decade, from 41 to 50 years, there were available for examination 13 tibial arteries, and these showed plainly an increasing degree of intimal sclerosis in the form of elastic splitting and subendothelial proliferation to form a distinct intimal collar. In contrast to the slight and moderate changes of the earlier decades, there are seen here marked intimal thickening, though this must be qualified as extreme for the tibial vessels. Not all these vessels showed marked change, 5 exhibiting moderate, and 8 marked alteration. Five of the 13 arteries (38.5%) also showed medial calcification. The sixth decade, from 51 to 60 years, furnished 14 tibial vessels for study and these showed approximately the same changes as seen in the previous decade, some arteries showing less and some more. In this period, there were 5 examples of medial calcification (35.7%). In the seventh decade, there were 14 tibials for examination, all of which showed intimal thickening,

8 of them marked. One of these vessels was occluded by an organized thrombus. Ten of the 14 vessels showed medial calcification (71.5%). Finally, there were 9 tibial arteries from subjects over 70 years, the oldest being 84. Eight of the 9 showed marked intimal thickening and 7 of the 9 medial calcification (77.8%). One vessel showed the only example of atherosclerosis in the series. Three of the 9 vessels after 70 were occluded by organized thrombi. There were thus 4 examples of tibial occlusion after 60 years of age, but all of these patients were free from definite signs or symptoms of obstruction. Of the 4 vessels showing organized occlusion, all exhibited medial calcification as well and in 1 of these the calcific change was in the form of bone formation.

Comparison of Tibial and Radial Arteries. If, now, this series of tibial arteries be compared with the radial arteries from the same patients, it will be noted that the mural changes are in a general way similar. That is to say, there first appears a splitting of the internal elastica, followed by further splitting and the development of longitudinally arranged, intervening connective tissue which increases progressively to finally and collectively form a distinct intimal collar. The amount of intimal change or sclerosis is slightly greater in the tibial artery. The difference, while not great, is usually recognizable in comparing sections of the two vessels from the same individual. It does not occur in every case and, in some instances, the radial thickening is about equal to that of the tibial or even a little greater. This feature was studied by observing the ratio of intimal thickness to medial breadth in both the radial and tibial sections. It was noted that in both the ratio of intimal to medial breadth was roughly at birth and in the first years 1 to 8. With thickening of the intima, this ratio was changed to 1 to 5 and later to 1 to 4 or 1 to 3. But when the radial ratio was 1 to 5, the tibial was not infrequently 1 to 4; and, further, when the radial ratio was 1 to 3, the tibial ratio was likely to be 1 to 2. In the seventh and eighth decades, the ratio was quite commonly 1 to 3 or 1 to 2 with the thickening slightly in favor of the tibial vessels. In comparing 57 tibial and radials, the thickening of the intima was about the same in 21, greater in the radial in 9 and greater in the tibial in 27. Of course, most of the sclerotic thickening occurs in the later years but it is especially after 60 years of age that the tibial forges ahead. Atherosclerosis was absent in the radials and was seen only once in the tibial series. As mentioned above, 4 of the tibial arteries showed organized occlusion; in the radials, there was no example of this change.

Medial calcification is a trait of the peripheral group of muscular arteries, but, as is well known, it is much more common in vessels of the lower extremities. In Lange's[9] series of 300 cases, medial calcification was present in the radial artery in 18% and the anterior tibial artery in 83% of cases. The radial and tibial arteries exam-

ined in this study were only short single segments and it might well be that calcification was present in other portions of the vessels and not in the particular small portion here studied. Nevertheless, Mönckeberg's sclerosis was observed in 14.7% of the 61 radials and in 47.5% of the 61 tibials. Calcification was not found in the radial vessels before 50 years of age, while there were 7 examples of tibial medial calcification in the 24 vessels from cases under 50 years. After 40 years of age, the radial percentage for calcification was 18 and tibial 54; after 50 years, the radials showed calcification in 24% and the tibial in 60% of cases; after 60, the radial percentage was 26 and the tibial 74. It will thus be noted that medial calcification was roughly about three times more common in the tibial than in the radial artery. It may further be observed that this change, even in the short fragment of artery examined, was present in over one-half the cases after 50 years of age and rose progressively in incidence with each decade. The location of the calcification, while usually plainly medial, in some instances appeared first at the intimal-medial border. Even here, it seemed to be basically medial. Medial calcification, even when extensive, was not necessarily associated with extensive intimal changes. On the contrary, vessels with marked calcification often showed less intimal involvement than the average for that age. Other medial findings, such as degenerative changes suggested by a pale blue-staining reaction and rarefaction of the muscle fibers, were occasionally seen and then more commonly in the tibial than the radial artery.

These changes are illustrated in Figures 1 and 2 which show pairs of radial and tibial arteries from the same individuals at various age periods. It is difficult in microphotographs of small arteries to show satisfactorily the intimal and other details which are so readily seen in observation through the microscope. The thickening of the intima is due to like changes throughout the age periods, only increasing in amount as age progresses, and so we have attempted to show here prominently only the two chief alterations, the amount of intimal thickening and the presence of calcification. This is done by blackening in the entire intima while calcification shows for itself.

Comparison of Tibial and Coronary Arteries. Comparing the tibial arteries with the coronary vessels from the same case, it was found, as in a comparison of the radial and the coronary, that the extreme arteriosclerotic and atherosclerotic changes common in the coronaries have no parallel in the relatively slight changes in the tibial vessels. In the extreme changes due to increasing age in the tibials, the ratio of intimal thickening to medial breadth was scarcely ever more than 1 to 2, while the ratio of breadth in the coronaries between the intima and media was, in the late decades, reversed and from 5 to 1 to 10 to 1 and accompanied by advanced athero-

sclerotic changes. As in the radial, the tibial artery in its histologic alterations through age and disease gives no hint of visceral sclerosis as typified in the coronary vessels. While there were slightly greater arteriosclerotic developments and certainly much more calcification in the tibial than in the radial, this had no inferential relation to coronary sclerosis.

In the 61 cases studied there were 6 cases of clinical coronary disease all of which showed narrowing and obstruction of the coronary arteries satisfactorily supporting the clinical evidence. But in addition there were 15 symptomless cases in which there were latent coronary lesions so extreme as to produce apparently complete or almost complete closure of the vessels. There was no hint of this in the condition of the corresponding 21 tibial vessels, for while it is true that many of these vessels showed marked calcification, it is also true that there were as many or more examples of tibial calcification in which the coronary arteries showed no extraordinary changes. This, of course, is nothing new, as it has been accepted for many years that Mönckeberg's sclerosis is a peripheral type independent of visceral changes.

Aside from the immediate subject, which is the comparison of a type peripheral artery with a type visceral vessel, the incidence and amount of coronary sclerosis in this series of cases seems of more than passing interest. While 50 of the 61 cases were past 40 and in what might be said to be the coronary period, it yet seems remarkable that 42% of those past 40 years of age and over 50% of those past 50 showed, from the viewpoint of pathologic histology, advanced coronary disease to the degree of apparently complete or almost complete occlusion of the vessel. There can hardly be any question as to the extreme mural alteration here but whether this produces the obstruction that the microscope suggests is questioned by Stewart, Birchwood and Wells,[14] who by distending with the usual pressure seemingly obstructed atherosclerotic coronary vessels found a fairly uniform lumen without evidence of constriction and conclude that "apparently the atherosclerotic plaques in coronary arteries do not necessarily protrude in the lumen during life and the apparent narrowings seen in the dead body may not have existed during life."

These sclerotic features are shown comparatively in Figure 3, which is not an exceptional but a type case. We have in our series many cases showing less radial and tibial alteration and as much or more coronary and other visceral scleroses than illustrated here. The patient was a male negro of 47 with advanced malignant hypertension and marked encephalopathy, dying with extensive cerebral softening. There was no history of coronary attack and no clinical diagnosis of coronary disease, the symptoms being almost exclusively cerebral. Attention is called to the extraordinary thinness of the media in the cerebral vessel, made recognizable by touching

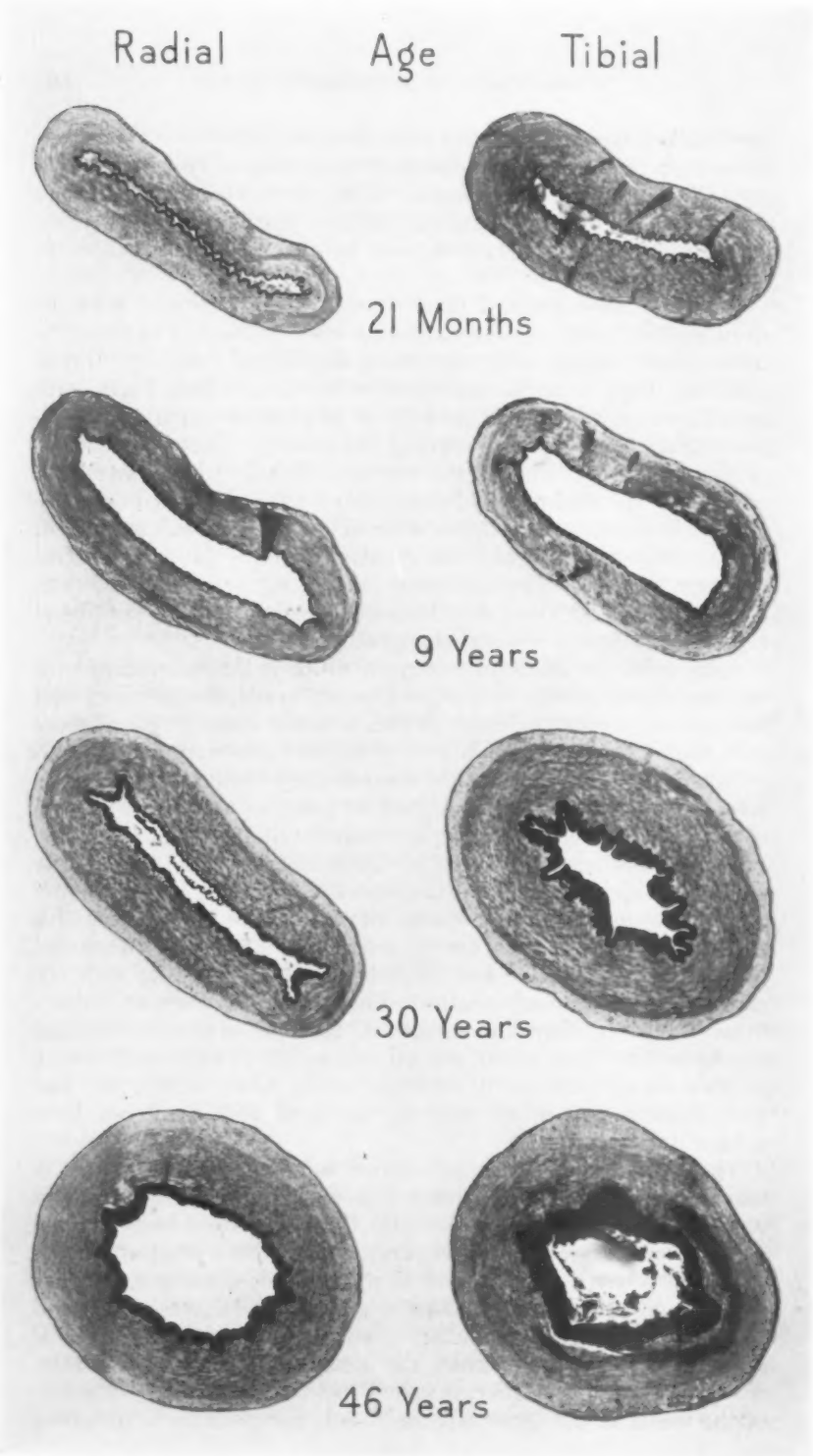


FIG. 1

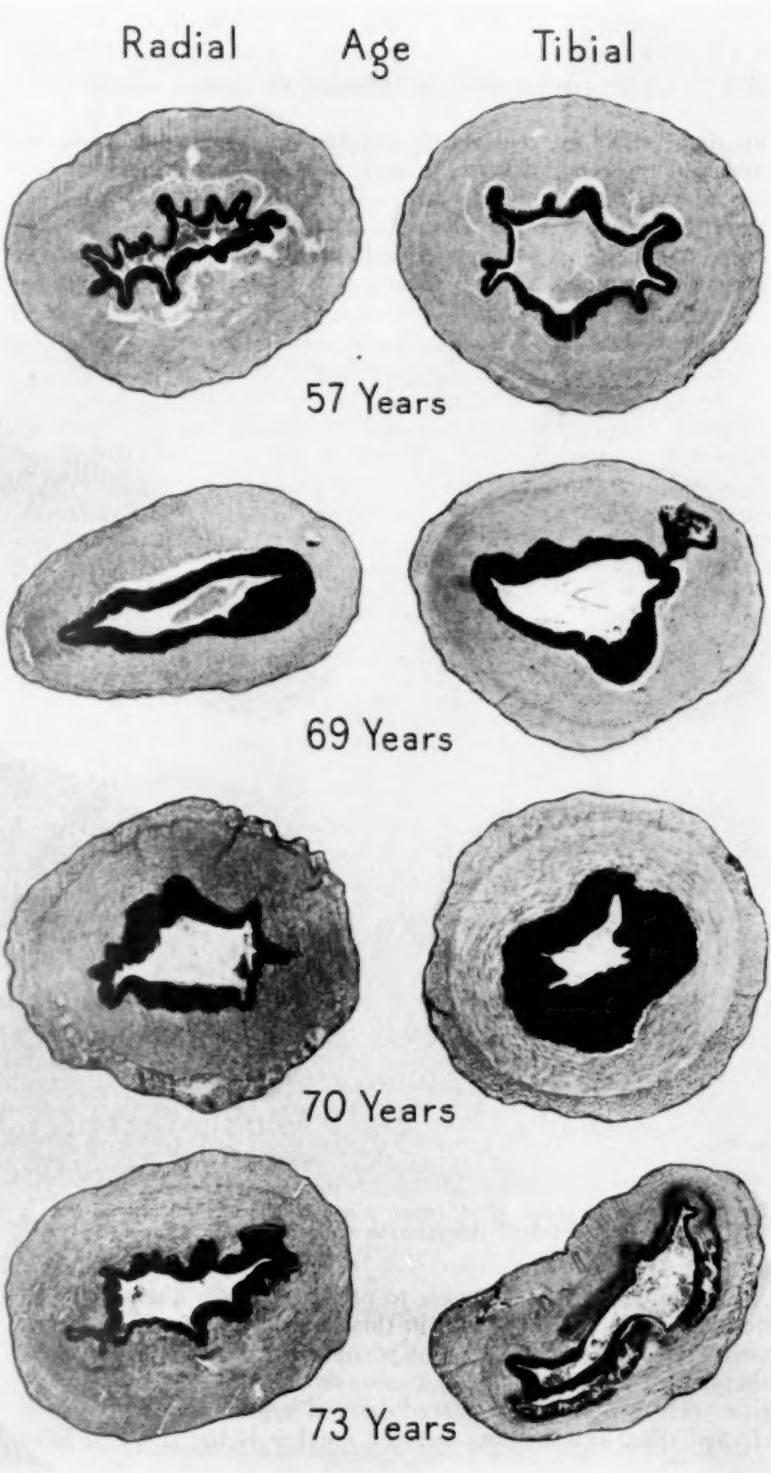


FIG. 2.

FIGS. 1 and 2.—Sections of radial and tibial arteries showing age period changes comparatively. (Hematoxylin and eosin stain, low power.) Intima blackened to show thickening distinctly.

up slightly the internal elastic membrane. This thinness of the media of the cerebral vessel is, as is well known, normal but it is probably partly pathologic here. The ratio of intimal to medial breadth in this vessel is 12 to 1. The intimal thickening of the radial and tibial vessels is more than usually seen in such condition and at such an age.

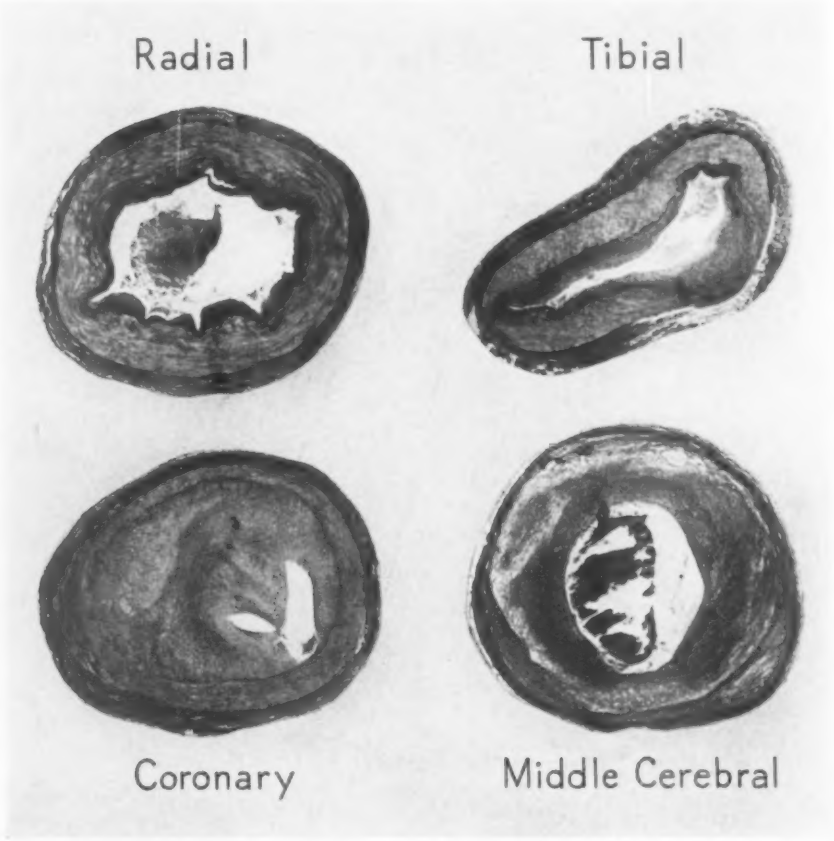


FIG. 3.—Sections of radial, tibial, coronary and middle cerebral arteries from a patient of 47 years. (Hematoxylin and eosin stain, low power.)

Examining the tibial vessels to observe specific disease effects, nothing significant was noted in this small series of cases. There were 7 cases of diabetes with no peculiar tibial, radial or coronary changes. Only 3 of the diabetic cases showed tibial artery calcification. There were 8 well-marked cases of hypertension, 7 of which showed tibial calcification, but the number is too small to have

meaning. The 4 cases showing organized occlusion of the tibial vessels were not diabetics.

Summary. Tibial artery age period changes and arteriosclerotic changes short of occlusive lesions consist of the development of a progressively thickening intimal collar of split elastica and longitudinally arranged interwoven connective tissue, together with more frequent and more voluminous medial calcification. These changes are similar to those found in the radials, but are slightly greater for the intima and decidedly greater for the media. Medial calcification was about three times more common in the tibial than in the radial in this series. Atherosclerosis is seldom a feature of tibial artery change. Altogether the intimal thickening in the tibial as well as the radial is slight, especially as compared with the coronary, and seldom threatens the integrity of the lumen. As in the radial, the anatomic condition of the tibial artery has no inferential bearing on coronary sclerosis.

REFERENCES.

(1.) **Bell, E. T.**: *in* Arteriosclerosis, E. V. Cowdry, Editor, New York, The Macmillan Company, p. 473, 1933. (2.) **Borcherdt, H.**: Virchow's Arch. f. path. Anat., **259**, 373, 521, 1926. (3.) **Bunge**: Arch. f. klin. Chir., **63**, 467, 1901. (4.) **Dietrich, K.**: Virchow's Arch. f. path. Anat., **274**, 452, 1929. (5.) **Ehrich, W., de la Chapelle, C. E.**, and **Cohn, A. E.**: Am. J. Anat., **49**, 241, 1931. (6.) **Gross, L., Epstein, E.**, and **Kugel, M.**: Am. J. Path., **10**, 253, 1934. (7.) **Hallenberger, O.**: Deutsch. Arch. f. klin. Med., **87**, 62, 1906. (8.) **Hesse, M.**: Virchow's Arch. f. path. Anat., **261**, 225, 1926. (9.) **Lange, F.**: Ibid., **248**, 463, 1924. (10.) **Lansbury, J.**, and **Brown, G. E.**: Proc. Staff Meet. Mayo Clin., **9**, 49, 1934. (11.) **Lundsgaard, C.**, and **Rud, E.**: Acta med. Scandin. (Suppl.), **26**, 558, 1928. (12.) **Nordmeyer, N.**: Beitr. z. path. Anat. u. allg. Path., **86**, 149, 1931. (13.) **Sappington, S. W.**, and **Cook, H. S.**: Am. J. Med. Sci., **192**, 822, 1936. (14.) **Stewart, J. D., Birchwood, E.**, and **Wells, H. G.**: J. Am. Med. Assn., **104**, 730, 1935. (15.) **Thayer, W. S.**, and **Fabyan, M.**: Am. J. Med. Sci., **134**, 811, 1907. (16.) **Warren, S.**: The Pathology of Diabetes Mellitus, 2d ed., Philadelphia, Lea & Febiger, p. 121, 1938. (17.) **Wolkoff, K.**: Virchow's Arch. f. path. Anat., **241**, 42, 1923; Beitr. z. path. Anat. u. z. allg. Path., **82**, 555, 1929.

THE REACTIVITY OF INTRACRANIAL VESSELS IN THE AGED.

By D. Ewen Cameron, M.D.,

NEUROLOGIST AND PSYCHIATRIST-IN-CHIEF, ALBANY HOSPITAL, ALBANY, N. Y.

AND

S. R. Rosen,* M.D.,

ASSISTANT PHYSICIAN, BOSTON PSYCHOPATHIC HOSPITAL, BOSTON, MASS.

(From the Department of Neurology and Psychiatry, Albany Medical College.)

A recent study (Cameron *et al.*)[2] from this Department showed that there was a strong probability that the cerebral oxygen consumption of patients suffering from psychoses of the senium was diminished. Since clearly the reactivity of the vascular system has a bearing upon the question of an adequate oxygen supply, an investigation of the integrity of this mechanism was undertaken in

* Formerly Resident in Neuropsychiatry, Albany Hospital, Albany, N. Y.

terms of the response of the systemic blood pressure to changes in position (Cameron *et al.*)[1]. It was found that the slight rise in blood pressure which usually follows upon rotating the cephalic end of the body upwards and the slight fall which follows upon rotating the same end downwards through small angles was frequently reversed in persons suffering from psychoses of the senium. In these persons the blood pressure tended to be more subject to purely mechanical factors, and in consequence the pressure tended to fall in the head-up position and tended to rise in the head-down position.

This latter study was informative as to the vasomotor control as a whole. Since, however, it is well known that vascular changes with advancing age often differ considerably in different parts of the body and may be quite advanced in the intracranial vessels and barely perceptible in the vessels of the rest of the body, a means was sought which would permit of estimating the reactivity of the intracranial vessels. Many agents produce considerable change in the caliber of the cerebral vessels. Among these are CO_2, which produces cerebral vasodilatation. Amyl nitrate also produces a definite vasodilatation. Caffeine is reported as causing cerebral vasoconstriction (Merritt and Fremont-Smith[5]). Administration of these agents is, however, hard to control with the necessary precision and, with the exception of the first, these substances do not occur normally in the organism. Histamine was finally selected as a possible preparation for further investigation.

The major action of this drug is to produce dilatation of the capillaries and also of the arterioles (Carrier[3]). With moderate dosages a fall in blood pressure is recorded, this occurring even though constriction of the arteries is present. It is believed that this fall in pressure is due to dilatation of the capillary bed (Sollmann[7]). The pulmonary artery also shows constriction, and, since histamine produces stimulation of smooth muscle regardless of its innervation, bronchial constriction has also been reported. It is clear that, if constriction of the pulmonary artery and of the bronchi took place, even with the minute doses of histamine which we propose to use, back pressure through the right heart and superior vena cava might occur; this, in turn, could, through interference with the venous return from the brain, cause an increase in spinal fluid pressure which might be difficult to distinguish from that produced by the dilatation of the intracranial vessels. This possibility was also investigated.

Since dilatation of intracranial vessels must result in a rise in spinal fluid pressure, it was decided to attempt to study the degree of reactivity of the smaller cerebral vessels by following the rise in spinal fluid pressure produced by the intravenous injection of a standard dose of histamine. While it is generally agreed (Merritt and Fremont-Smith[5]) that the Monro-Kellie doctrine of the cranium

as a rigid container can no longer be held, yet we regard it as probable that the amount of elasticity existing in the container represented by the cranium and the spinal subarachnoid space is not so great as to preclude our being able to estimate with reasonable accuracy the relative reactivity of the vessels of the aged and the younger adult brain.

Procedure. Lumbar puncture was carried out in the lateral recumbent position. Spinal fluid pressure readings were obtained by the use of a water manometer. The pressure was recorded at minute intervals until all trends had disappeared for 10 consecutive minutes. Then 0.00025 mg. of histamine phosphate per kilo body weight was injected into an antecubital vein. Since insertion of the needle usually results in a rise in spinal fluid pressure, actual injection of the histamine was withheld until the pressure had returned to its former level. Immediately following the injection, spinal fluid pressure readings were recorded every 15 seconds for 2 minutes, at the end of which time the reaction had in the majority of cases ceased. The pulse, blood pressure and respiratory rates were recorded on the first 20 patients throughout their reaction, but, since there was no constant variation, further recording was discontinued. These studies were carried out on 38 patients suffering from psychoses of the senium and in 53 patients whose ages ranged from 20 to 50, who were suffering from early schizophrenia, alcoholism, manic-depressive states, psychoneuroses or psychopathic states.

In order to throw light on the question of whether the dosages of histamine which we employed were sufficiently large to produce bronchial spasm, constriction of the pulmonary artery and, consequently, back pressure in the venous system, we investigated the venous pressure levels concurrently with the spinal fluid pressure changes in response to the injection of a standard dose of histamine. The venous pressure readings were obtained by means of an apparatus similar to that described by Moritz and von Tabora.[6] The venous records were taken from an antecubital vein. Simultaneous venous and spinal fluid pressure readings were taken before injection and at 5-second periods for 2 minutes after injection of the histamine. This procedure was carried out on 8 occasions in 5 patients, the group including both old and younger individuals.

Results. It can readily be seen from Table 1 that there is no tendency for histamine in the amounts used to raise the venous pressure. In the 8 investigations of this point an increased venous pressure was found on only one occasion. It was noted moreover that the rise in venous pressure persisted in this instance after spinal fluid pressure had returned to its basic level.

TABLE 1.—EFFECTS OF HISTAMINE PHOSPHATE (0.00025 MG. PER KG. BODY WEIGHT) ADMINISTERED INTRAVENOUSLY UPON SPINAL FLUID AND VENOUS PRESSURE.

Seconds.	Spinal fluid pressure.	Venous pressure.
15	+ 9	−1.75
30	+ 47	−2.25
45	+118	−6.25
60	+ 60	−5.00
75	+ 34	−3.75
90	+ 24	−4.75
105	+ 7.5	−5.00
120	+ 2.5	−4.00

Figures represent average rise or fall in terms of millimeters of water in 8 checks on 5 persons.

The data concerning the response of the spinal fluid pressure in the control group early showed that those patients who suffered from alcoholism showed a special type of response. Accordingly, the responses of the senile, alcoholic, and the remainder of the control group, which was designated the indeterminate group, are recorded separately in Table 2.

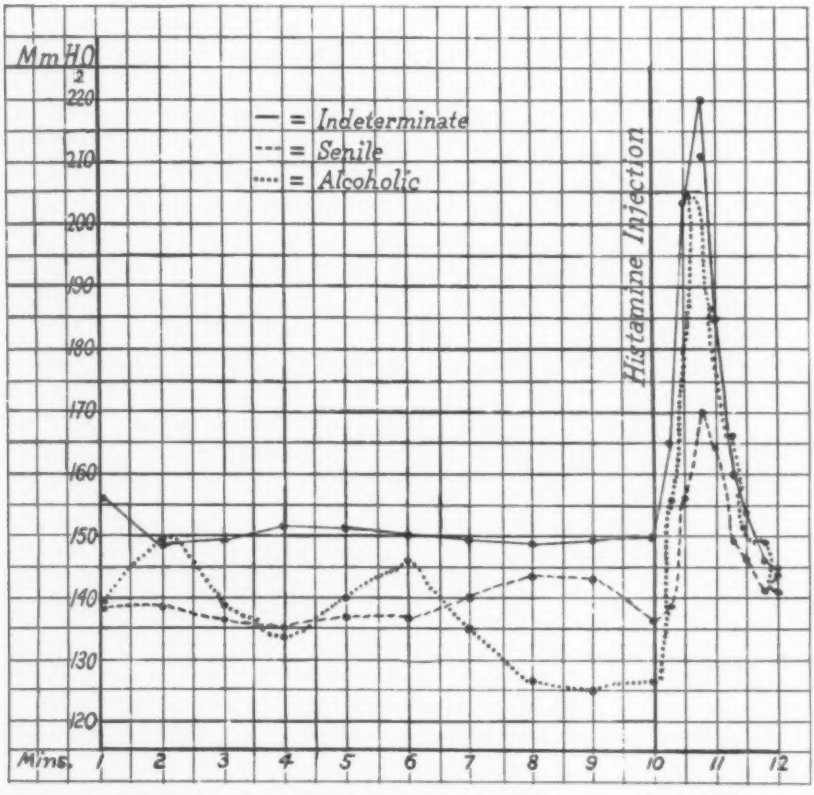


CHART 1.—Effects upon the spinal fluid pressure of histamine phosphate (0.00025 Mg. per kg. body weight) administered intravenously.

In all 3 groups the maximum rise is reached during the 45 seconds reading and in all save the alcoholics the spinal fluid pressure had returned to approximately normal levels by the 105th second. The prehistamine level was not attained in the case of the alcoholic group by the 120th second. The average rise in the indeterminate group was 70 mm. water; in the senile group it was strikingly less, being only 34 mm. water; the alcoholic group was characterized by a higher average rise, namely, 86 mm. water (Chart 1).

TABLE 2.—RANGE OF SPINAL FLUID PRESSURE RESPONSES TO HISTAMINE EXPRESSED IN TERMS OF RISE OVER BASAL LEVEL.

Pressure (mm. H_2O).	Per cent of cases in each category.		
	Senile.	Indeterminate.	Alcoholic.
0–20	18.91	4.34	0
21–40	29.72	8.69	7.69
41–60	8.10	39.13	7.69
61–80	13.51	8.69	23.07
81–100	10.81	13.04	23.07
101–120	8.10	13.04	15.38
121–140	5.40	8.69	7.69
141–160	0	0	7.69
161–180	0	0	0
181 up	5.40	4.34	7.69

Considerable overlap occurred, as is shown in Table 2. Two of the indeterminate group had rises of less than 34 mm. water, and 8 had rises of more than 86 mm. water; 15 of the senile group had rises of more than 70 mm. water and 8 had rises of more than 86; in the alcoholic group, 8 had rises of less than 70 mm. water, and 1 had a rise of less than 34.

Discussion. It is clear that, if we consider the senile group as a whole, there is a definite diminution of reactivity of the cerebral vessels as contrasted with that found in the younger group. The fact that considerable range of reactivity occurs within the senile group renders it possible to anticipate that by means of this method of approach an attempt may be made to differentiate groups within the senium, in which the major disability consists in a loss of reactivity of the cerebral vessels from groups in which this reactivity is relatively well preserved.

The fact that limited reactivity may be met with in younger age groups must await further study before a final explanation can be given. Clearly, one must consider the possibility that it may be ascribable to the abnormal psychiatric condition from which the individual was suffering; it may, on the other hand, be quite independent of this and represent the amount of variation usually found within a series of subjects. If the latter is the case, one may suggest that, while relatively little reactivity of the cerebral vessels may permit of adequate cerebral functioning during younger adult years, this limitation may become of more serious moment later on when a slower circulation time, a diminished cardiac output and a lowered blood oxygen-carrying power begin to result in chronic cerebral anoxemia.

The increased reactivity of the alcoholic group is rather difficult to explain. It is noted, however, that considerably more difficulty was experienced in obtaining a steady base line in the alcoholic group. This was due to the amount of emotional tension. It seems possible that this tension may also be accountable for the increased rise in the spinal fluid pressure in response to histamine. In this connection it should not be forgotten that it has been reported that

there is pathological evidence to suggest that excessive alcoholic indulgence tends to reduce the probability of arteriosclerosis (Leary[4]).

Summary. 1. A method is reported for investigating the reactivity of the cerebral vessels by observation of the spinal fluid pressure changes after intravenous injections of histamine.

2. A series of 38 senile and 55 psychiatric patients at younger age levels was examined.

3. The average rise in spinal fluid pressure in the senile group was 34 mm. of water; the average for 29 alcoholics included in the younger group was 86 mm. of water; and the rise for the 26 remaining patients in the younger group was 70 mm. of water.

4. The bearing which this may have on possible cerebral anoxemia in the aged was considered.

REFERENCES.

(1.) **Cameron, D. E., Mele, D.,** and **Hirst, H. S.**: Effects of Position Upon the Brachial Blood Pressure in the Senium (in press). (2.) **Cameron, D. E., Rosen, S. R., Fazekas, J.,** and **Himwich, H. E.**: Am. J. Psychiat., **97**, 566, 1940. (3.) **Carrier, E. R.**: Am. J. Physiol., **61**, 528, 1922. (4.) **Leary, T.**: New England J. Med., **205**, 231, 1931. (5.) **Merritt, H. H.,** and **Fremont-Smith, F.**: The Cerebrospinal Fluid. Philadelphia, W. B. Saunders Company, 1937. (6.) **Moritz, F.,** and **von Tabora, D.**: Deutsch. Arch. f. klin. Med., **98**, 475, 1910. (7.) **Sollmann, T.**: A Manual of Pharmacology, Philadelphia, W. B. Saunders Company, 1934.

THE EFFECT OF PREGNANCY UPON EXPERIMENTAL HYPERTENSION IN THE RABBIT.*

By John D. Corbit, Jr., M.D.,

ASSISTANT INSTRUCTOR IN OBSTETRICS AND GYNECOLOGY, SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA, PHILADELPHIA, PA.

(From the Department of Obstetrics and Gynecology, University of Pennsylvania.)

Women afflicted with chronic arterial hypertension usually suffer some aggravation of their disease if they become pregnant. No satisfactory explanation has yet been offered for this unfavorable influence of pregnancy. One obvious means of studying this phenomenon is afforded by observing the blood pressure during pregnancy in animals previously made hypertensive by the experimental induction of renal ischemia, for it is believed that the latter plays a rôle in at least several of the forms of chronic hypertension observed in child-bearing women (Goldblatt[2]).

Harrison, Grollman and Williams,[5] found that gestation tends to lower the level of a pre-pregnancy hypertension in rats.† This result is the reverse, therefore, of what might have been anticipated from clinical experience. That such a finding is probably to be

* Aided by a grant from the Commonwealth Fund.

† Since this article was submitted for publication, two others have appeared which must be mentioned here. Page, *et al.*[6] report that pregnancy brings about a lowering of blood pressure in both the rat and rabbit, and Dill, *et al.*[1] failed to find any alteration in blood pressure during repeated pregnancies in rabbits.

expected among laboratory animals is suggested by the observations of others. Thus, Pickering and Prinzmetal[7] did not note any unfavorable effort of pregnancy upon chronically hypertensive rabbits, and Goldblatt[3] found that during pregnancy, most hypertensive dogs exhibited a slight or moderate fall of pressure. It is noteworthy, however, that no information is available concerning the effects of pregnancy upon the arterial tension of normal animals. For this reason we have investigated the influence of pregnancy upon both normal and renal ischemic rabbits.

Materials and Methods. Observations were made upon does of miscellaneous racial stocks for periods ranging from 3 to 6 months. Only healthy, mature animals, of proven fertility, and weighing more than 2.5 kg. were studied. They were housed in individual cages, and were fed a standard complete ration in the form of pressed dry pellets.* Body weight was taken at weekly intervals.

Blood pressure determinations were made once weekly, except during pregnancy, when they were made twice a week or daily. The ear-capsule method of Grant and Rothschild[4] was used. For this purpose the animals were trained to lie quietly upon an electrically warmed pad without the use of a restraining harness. A period of 2 to 3 weeks was utilized in accustoming each animal to this technique. Pressures were recorded only when determinations, made at consecutive 30-second intervals, were constant to within 4 mm. of Hg.

Blood samples were taken once weekly by arterial puncture and analyzed for blood urea nitrogen by the method of Van Slyke and Cullen.[9] Blood uric acid determinations also were run on these samples, but since no significant variations were noted, these results have not been included in the data which follow. Specimens of urine were collected at weekly intervals and analyzed for protein by a quantitative technique.[8]

Varying degrees of renal ischemia were produced in 16 animals by the method of Pickering and Prinzmetal.[7] A clamp was applied to the left renal artery, and after an interval of 3 to 10 days, the right kidney was removed. Effort was made to obtain 2 types of result: *a*, persistent arterial hypertension, and, *b*, a borderline grade of ischemia insufficient to produce an elevation of blood pressure, or at most, sufficient to cause only a transient hypertension. The latter group was studied in the expectation that pregnancy might unmask a hypertension which was presumably latent under these conditions; in the event of failure to do so, these animals could be utilized as blind operation controls. In the animals operated upon, a period of 10 to 12 weeks was allowed to elapse, and any elevations of pressure were permitted to become stabilized, before the animals were mated.

In addition to observations made upon normal non-pregnant animals for the purpose of establishing control data, the studies concerning the effects of pregnancy include data derived from 21 animals, as follows: *a*, 5 intact normal rabbits; *b*, 11 rabbits in which the attempt to produce renal ischemia had resulted in no elevation, or only transient elevation, of blood pressure, and in which the arterial tension was therefore essentially normal at the time of mating; and, *c*, 5 rabbits in which the operative procedures had resulted in a conspicuous elevation of blood pressure, maintained at hypertensive levels for at least 3 weeks prior to mating.

Observations. *Prior to Pregnancy.* Data concerning the levels and fluctuations of blood pressure and blood urea, and the incidence of proteinuria among non-pregnant does, are summarized in Table 1.

* Supplied as Rockland Rabbit Ration and containing 17% protein.

TABLE 1.—RENAL ISCHEMIA IN RABBITS.

(Systolic blood pressure, blood urea nitrogen and proteinuria in non-pregnant does, observed for periods of 1 to 3 months.)

Animals.	Blood pressure.		Blood urea nitrogen.		Proteinuria.	
	Determinations.	Mean, mm. Hg.	Determinations.	Mean, mg. per 100 cc.	Urine exams.	Positive.
Normal (17) . .	176	80.0 ± 4.8	46	16.4 ± 2.9	10	3
Ischemic, non-hypertensive (11) . .	91*	85.7 ± 9.2	14*	24.4 ± 4.7	13	5
Ischemic, hypertensive (5) . . .	50*	128.6 ± 12.0	14*	23.4 ± 3.7	18	11

* Determinations made after the B.P. had become stabilized in its permanent postoperative range.

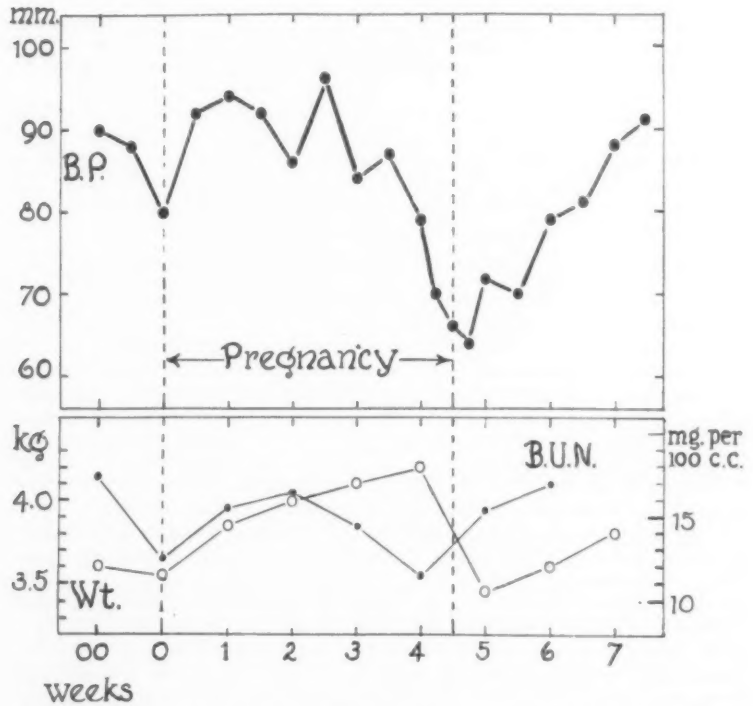


CHART 1.—*Normal Rabbit 709.* Effect of pregnancy upon systolic blood pressure (B.P.), body weight (Wt.) and blood urea nitrogen (B.U.N.). This rabbit delivered 8 living pups at term. Note the sharp fall in blood pressure just before delivery and the gradual return to normal during the postpartum period. The B.U.N. variations noted here are characteristic of the control group and are not great enough to be considered significant.

The blood pressure of normal rabbits was found to be remarkably constant from day to day. Although slight individual variations occurred, the mean pressure of 17 healthy does was 80±4.8 mm. Hg. The blood urea nitrogen was likewise found to be fairly constant at a level of 16 mg. per 100 cc. Proteinuria was observed in about one-third of the urine specimens examined.

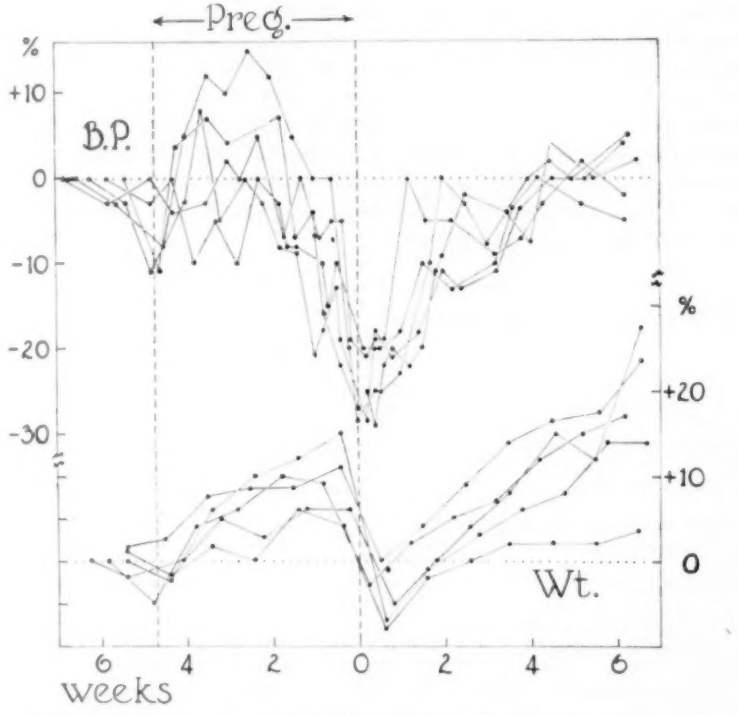


CHART 2. *Pregnancy in normal rabbits.* Per cent change of systolic blood pressure and body weight from pre-pregnancy levels in a group of 5 healthy animals. The average of 3 blood pressure determinations made during the 3 weeks prior to mating is taken as 100%. Every animal had a significant fall in pressure at time of delivery.

Among the 11 animals operated upon in which the experimental procedures failed to bring about permanent elevation of blood pressure, there were few features serving to distinguish them from healthy intact animals. They exhibited a slight persistent elevation of blood urea nitrogen, and a tendency to excrete protein in the urine. Their general health remained good, however, as evidenced by a gain of body weight and by their readiness to accept the buck at the time of mating.

The 5 animals with persistent hypertension exhibited a mean pressure of 130 mm. of Hg. Otherwise their condition resembled in

every particular that of the group described in the preceding paragraph.

Pregnancy. The changes in a typical normal rabbit are illustrated in Chart 1. Chart 2 demonstrates the constancy of these changes among normal rabbits, and the data of Table 2 indicate their extent. Thus, it was found that pregnancy caused no appreciable alteration in the systolic blood pressure until the last 7 days of gestation. During that time, a significant and constant fall was noted. This drop, which was usually equivalent to over 20% of the pre-pregnancy tension, reached its maximum at or shortly following labor. This low pressure returned to the pre-pregnancy level quite gradually, during the first 2 to 3 weeks post partum. These changes of pressure were accompanied by no evidences of ill health, since the coincidental changes in body weight, as well as the duration of pregnancy and size of litters, were normal. The blood urea levels during pregnancy showed no significant fluctuations.

TABLE 2.—RENAL ISCHEMIA IN RABBITS.

(Influence of pregnancy upon body weight, systolic blood pressure and blood urea nitrogen.)

Animals.	Mean body weight, kg.	Mean blood pressure, mm. Hg.	Mean blood urea N, mg. per 100 cc.	Proteinuria.
Normal (5):				
Beginning of pregnancy	3.6	82	16	1
Term	4.0	64	15	0
2 wks. postpartum	3.7	83	14	3
Ischemic, non-hypertensive (11):				
Beginning of pregnancy	4.4	88	25	3
Term	4.5	71	19	9
2 wks. postpartum	4.3	81	23	8
Ischemic, hypertensive (6):				
Beginning of pregnancy	4.2	126	22	2
Term	4.4	97	19	4
2 wks. postpartum	4.3	126	21	3

Entirely analogous changes were observed among the 11 animals operated upon whose blood pressures were normal at the time of mating. The only characteristic exhibited by this group, and not seen in normal rabbits, was a tendency of the blood urea to fall at the end of pregnancy. This was not infrequently accompanied by proteinuria.

The same changes were also exhibited by the 5 hypertensive rabbits. A typical protocol is illustrated in Chart 3. Both Chart 3 and the data in Table 2 indicate that the hypertension which was present at the beginning of pregnancy in this and in the remaining animals, was not accompanied by elevations of blood urea which could be considered uremic in character. Not only did pregnancy fail to aggravate the chronic hypertension of these animals, but, as in the control groups, it depressed the level of both the

pre-pregnancy blood pressure and blood urea nitrogen. The depressions, moreover, were of the same order as they were among the control animals.

In only one instance were the results otherwise than as described. In Rabbit 5, whose protocol is illustrated in Chart 4, the pre-labor fall of blood pressure was cut short at the 28th day of gestation. Thereafter, it rose rapidly and continued to do so throughout the

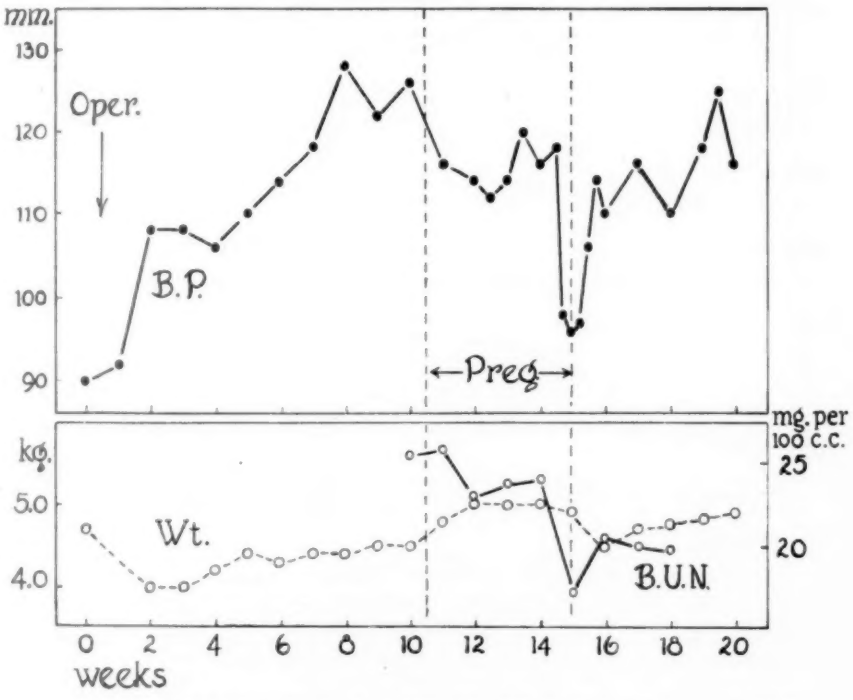


CHART 3.—*Renal hypertension in Rabbit 428.* Effect of pregnancy upon systolic blood pressure, body weight and blood urea nitrogen. This animal delivered 8 living pups at term. Note that the degree of pressure fall is similar to that in the normal animal (Chart 1) and that the fall is sharp near the time of delivery with a more gradual return to normal during the postpartum period. The decrease in level of B.U.N. at or near term was constant in this group.

remainder of pregnancy and the ensuing post-partal period. The later stages of this rise were accompanied by uremia, from which the animal ultimately succumbed on the 10th post-partal day. It is noteworthy that the pups of this animal were macerated and subnormal in weight, indicating that intra-uterine death had probably occurred at about the time in pregnancy when the unusual sequence of events was initiated.

Miscellaneous Observations. Table 3 indicates that the average duration of pregnancy and the size of the litters in all groups were normal.

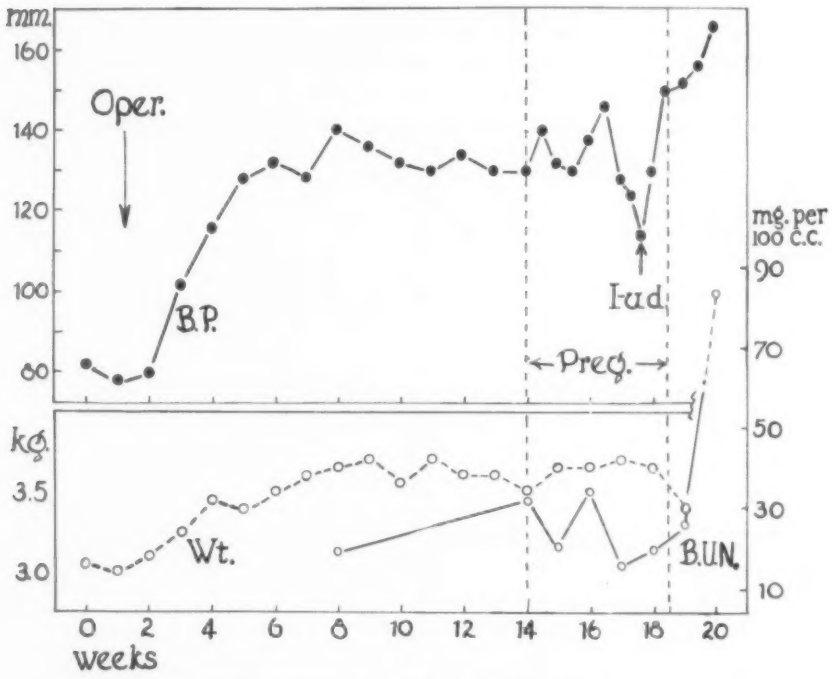


CHART 4.—*Renal hypertension in Rabbit 5.* Effect of pregnancy upon systolic blood pressure, body weight and blood urea nitrogen. Intra-uterine death (I-ud) of fetuses? We believe that there is a reasonable evidence that the pups in this case died about the time the blood pressure ceased to fall and suggest that the presence of viable pups temporarily delayed the ultimate course of events.

Analysis of our data indicates that the extent of the pre-labor fall in blood pressure among the various groups of animals was closely related to the number of fetuses present *in utero*. This relationship is illustrated in Chart 5.

TABLE 3.—RENAL ISCHEMIA IN RABBITS.

(Data concerning pregnancy.)

Animals.	Average duration of gestation, days.	Average size of litters, pups.
Normal (5)	32.2	6.4
Ischemic, non-hypertensive (11)	31.7	5.4
Ischemic, hypertensive (6)	32.8	5.7

Discussion. Our results confirm the previous observations that pregnancy does not aggravate the arterial hypertension which can be produced in experimental animals by the induction of renal

ischemia. This failure to produce an experimental result incorporating the features of a syndrome observed in clinical medicine is probably due to one of two facts: Either the nature of this experimental hypertension differs from that seen in the child-bearing woman, or the physiology of pregnancy in the rabbit, dog and rat differs in those particulars which account for the pressure changes observed in the human.

Our data, moreover, show that the fall in arterial tension which pregnancy causes in hypertensive animals can also be demonstrated in non-hypertensive animals. Since this observation has not been

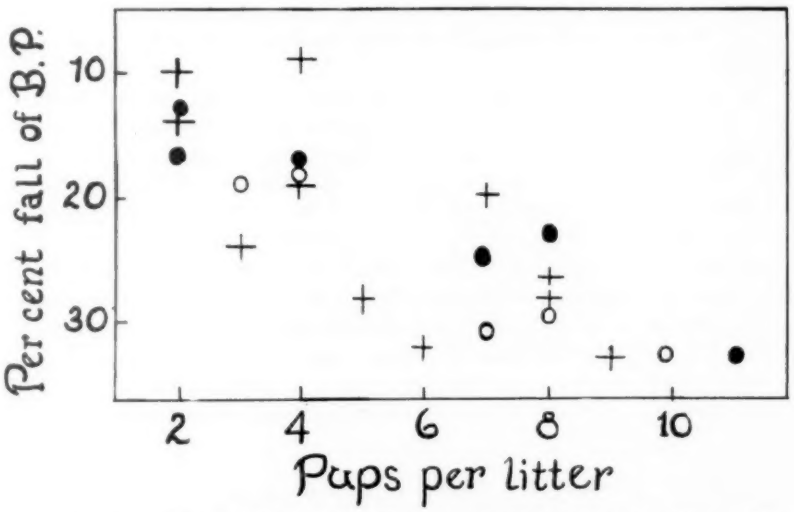


CHART 5.—*Per cent fall of maternal blood pressure in relation to size of litter.* O = normal rabbits. + = ischemic, non-hypertensive rabbits. ● = hypertensive rabbits. Calculated as the per cent difference between the level during the pre-pregnancy control period and the last pressure recorded before the onset of labor. Note that the fall of pressure is greater as the number of pups per litter increases and that it is of the same general order regardless of surgical procedures or pre-pregnancy level.

made previously, it is necessary that caution be exercised in ascribing to pregnancy any specific beneficial effect upon experimental hypertension. The production during pregnancy of a specific antipressor substance cannot be postulated in the light of these results, unless there is evidence that the pressor substance which it presumably neutralizes is a factor in the maintenance of normal arterial tension.

The nature of the mechanism which brings about the pre-partal fall of pressure is obscure. While it is apparently concerned with the number of fetuses *in utero* at the time the fall occurs, any assumption that a humoral factor elaborated by the products of conception

is responsible, or that local hemodynamic factors are the cause, must be examined in the light of the fact that the depression is maintained for a prolonged period following delivery.

Summary. A study was made of the fluctuations in: *a*, blood pressure; *b*, blood urea; and, *c*, in the excretion of urinary protein during pregnancy in normal rabbits, and in rabbits in which arterial tension was previously raised by the experimental induction of renal ischemia.

It was found in both groups of animals that pregnancy tended to bring about a lowering of the systolic pressure a few days before the onset of labor. The extent of this fall amounted to about 20% of the pre-pregnancy tension. The return of pressure to the pre-pregnancy level occurred gradually during the first 2 to 3 weeks post partum.

In the normal animal these fluctuations of arterial tension were not accompanied by significant alterations of blood urea, nor by proteinuria. In the renal ischemic animals, however, there was a coincidental, slight, pre-partal fall of blood urea, and a tendency to proteinuria. In no animal was there evidence to indicate that these changes were due to ill health. The normal gestational increase of maternal body weight took place, the pregnancies were normal in duration, and the number of pups born was normal for this species.

The extent of the pre-partal fall of blood pressure was proportionate to the number of fetuses present.

It is a pleasure to acknowledge the capable assistance of Miss Isabella Fullerton and of Miss E. H. Shiels, of the Department of Pharmacology, who performed the chemical determinations.

REFERENCES.

(1.) **Dill, L. V., Isenhour, C. E., Cadden, J. F.,** and **Kuder, A.**: Surg., Gynec., and Obst., **72**, 38, 1941. (2.) **Goldblatt, H.**: Am. J. Clin. Path., **10**, 40, 1940. (3.) **Goldblatt, H., Kahn, J. R.,** and **Hanzal, R. F.**: J. Exp. Med., **69**, 649, 1939. (4.) **Grant, R. T.,** and **Rothschild, P.**: J. Physiol., **81**, 265, 1934. (5.) **Harrison, T. R., Grollman, A.,** and **Williams, J. R.**: Am. J. Physiol., **128**, 716, 1940. (6.) **Page, E. W., Patton, H. S.,** and **Ogden, E.**: Am. J. Obst. and Gynec., **41**, 53, 1941. (7.) **Pickering, G. W.,** and **Prinzmetal, M.**: Clin. Sci., **3**, 357, 1938. (8.) **Shevky, M. C.,** and **Stafford, D. D.**: Arch. Int. Med., **32**, 222, 1923. (9.) **Van Slyke, D. D.,** and **Cullen, G. E.**: J. Biol. Chem., **24**, 117, 1916.

FIBRILLARY TWITCHINGS.

AN INVESTIGATION OF THEIR SITE OF ORIGIN.

BY C. HUNTER SHELDEN, M.D.,

AND

HENRY W. WOLTMAN, M.D.,

SECTION ON NEUROLOGY, MAYO CLINIC, ROCHESTER, MINN.

FOR many years it has been commonly believed that fibrillary twitchings are caused by irritation or degeneration of the cells of the anterior horn of the spinal cord. This hypothesis, like many

other hypotheses in medicine, has been stated so repeatedly that it has become accepted as a fact, even though it has no better basis than the frequent association of fibrillary twitchings with neurologic diseases in which there is evidence of a lesion of the spinal cord. Fibrillary tremors are helpful in the recognition of such diseases, but they also occur in other conditions, some of them harmless and not, so far as is known, resident in the central nervous system. The exact mechanism of production of fibrillary twitchings in muscles has never been accurately described.

One of the most informative contributions was that of Denny-Brown and Pennybacker.[1] According to these authors, beginning on the fifth day after denervation of a muscle, a fine fibrillation may be seen. This is associated with a particular sensitivity to acetylcholine. These authors also found, in cases of amyotrophic lateral sclerosis, bulbar palsy and progressive muscular atrophy, that a fibrillary twitch was accompanied by a single large action current. This was determined by means of a needle electrode and appropriate recording devices. The group of fibers involved in the "fasciculation" is smaller than a muscle fasciculus, but much larger than a single muscle fiber. The only functional group of this nature in muscle is the motor unit. Denny-Brown and Pennybacker inferred from their observations and the pathology of the disease that the disorder underlying fasciculation was situated in the nerve fiber or in the parent cell of the anterior horn, probably the latter.

Our desire was to determine whether or not the current idea of the central origin of fibrillation in such diseases as progressive muscular atrophy, progressive bulbar paralysis and amyotrophic lateral sclerosis was correct, or whether there was some peripheral mechanism at work which accounted for the fibrillation. Investigation of this point alone seemed simple, as one had only, by some mechanical means, to interrupt the nervous pathway between the cells of the anterior horn and the involved muscle. It seemed logical that if, by means of some anesthetic agent, the intervening nerve pathway was interrupted and fibrillation continued, one could assume that there was some peripheral mechanism wholly or in part responsible for the development of the fibrillation.

Protocol. An elderly man who registered at this clinic in February, 1940, suffering from amyotrophic lateral sclerosis with generalized fibrillary twitchings in both lower extremities, was desirous of having us carry out any type of investigation which might throw some light on the etiologic factors responsible for his condition. To effect spinal anesthesia, 70 mg. of procaine in 2 cc. of cerebrospinal fluid was administered. Complete motor and sensory paralysis was obtained well above the level of the umbilicus. Biopsy of the left gastrocnemius muscle was carried out while anesthesia persisted. It was clearly seen that the fibrillary twitchings in the exposed and other muscles continued unchanged. A few days later, peripheral

block of the left common peroneal nerve was done, using metycaine (benzoyl-γ-[2-methylpiperidino]-propanol hydrochloride). In spite of the complete foot drop and complete peroneal anesthesia, there was no visible change in the diffuse fibrillary twitchings of the involved peroneal muscles.

The observations of Denny-Brown and Pennybacker would seem to require, in the explanation of "fasciculation" at least, some activity on the part of the motor neuron. Our observations of a patient with amyotrophic lateral sclerosis, and also of another patient with the same disease, would seem to exclude the bodies of the cells of the anterior horn as the site of involvement, as fibrillation in the lower extremities persisted under the influence of spinal anesthesia or block of the nerve to an involved area. Indeed, the observations suggest some alteration in the response of the neuromuscular unit at its periphery, presumably to a chemical agent. Although these observations do not explain the phenomenon of fibrillation, they indicate that future studies of fibrillation should be addressed to the peripheral portions of the neuromuscular unit rather than to the cell body itself.

REFERENCE.

(1.) **Denny-Brown, D.**, and **Pennybacker, J. B.**: Brain, **61**, 311, 1938.

ANIMAL EXPERIMENTS CONCERNING THE HORMONAL THERAPY OF TESTICULAR ATROPHY.*

By Hans Selye, M.D., Ph.D.,
ASSISTANT PROFESSOR IN HISTOLOGY,
AND
Sydney M. Friedman, M.D.,
DEMONSTRATOR IN HISTOLOGY,
MONTREAL, CANADA.

(From the Department of Anatomy, McGill University.)

In previous communications we endeavored to show that both in the male and in the female, the gonad-stimulating actions of androgens and estrogens are direct, peripheral effects while the gonad-inhibitory actions of these same compounds are indirect and merely the result of an inhibition of gonadotropic hormone production by the hypophysis[2a,b]. The view was also expressed that the reason why the same steroid may either inhibit or stimulate the gonad depending on the dosage used, is simply that the optimal dosage range for the direct (stimulating) and the indirect (inhibitory) effect is not the same. In the same experimental series, we

* The expenses of this investigation were defrayed by a grant in aid received from the Schering Corporation of Bloomfield, N. J.

also noted that the gonadal atrophy produced by a number of agents, which presumably suppress gonadotropic hormone production by the pituitary, can be inhibited by treatment with such doses of steriod sex hormones as are required for the direct stimulation of the gonad. It seemed of interest to extend these experiments to such instances of gonadal atrophy which are known to result from direct damage to gonadal tissue and not merely to suppression of gonad-stimulating pituitary activity. In the present communication, we report experimental evidence in which the action of androgens was studied after testicular damage produced by cryptorchidism or Roentgen ray treatment of the gonad itself.

Experiment 1: Five groups of 6 young male albino rats of an average body weight of 58 gm. were treated as follows: Two groups were irradiated, two were rendered bilaterally cryptorchid, and the final group served as untreated controls. Three weeks later, daily subcutaneous treatment with 10 mg. testosterone in 0.4 cc. of peanut oil was initiated in one group of irradiated and one group of cryptorchid animals and continued for 21 days. On the day after the last injection, all animals were sacrificed and the organs taken for weight and histological study. The method of irradiation was as follows: Under nembutal (pentabarbital sodium) anesthesia, the animals were laid on their backs, shielded with lead, only the scrotum and lower limbs being exposed. Radiation to a total of 800 r was given (at 110 KV, 0.7 ma, through 1 mm. Al) within 15 minutes. This dosage was chosen as being that most likely to produce complete but not irreparable atrophy.[1] Table 1 summarizes the data.

TABLE 1.—EFFECT OF DELAYED TESTOSTERONE TREATMENT ON TESTES DAMAGED BY ROENTGEN RAYS OR CRYPTORCHIDISM.

Treatment.	Testes wt.*	Single testis wt.		Sem. ves.	Prost.	Histology.
		In scrotum.	In abdomen.			
Untreated	2.214	1.107	...	0.266	0.421	Normal histologic structure
Irradiated	0.606	0.303	...	0.245	0.334	Inhibition of spermatogenesis; Leydig cells large
Irradiated plus testosterone	0.444	0.223	...	1.034	0.721	Inhibition of spermatogenesis; Leydig cells atrophic
Cryptorchid	1.250	0.878 (3)	0.372 (5)	0.247	0.320	Inhibition of spermatogenesis; Leydig cells large
Cryptorchid plus testosterone	1.008	0.762 (3)	0.246 (3)	1.285	0.823	Inhibition of spermatogenesis; Leydig cells atrophic

* Since in some cases descent of one testis occurred in the cryptorchid groups, the weights of these intraabdominal testes are compared with the weights for single testes in other groups. The number of testes on which the average weight is based is given in parentheses.

The Roentgen ray conditioned atrophy was fairly complete as shown by the testis weight of 0.606 gm. as compared with 2.214 gm. in the normal. Testosterone was ineffective in restoring the testis

to or towards normal, indeed the testes of the treated animals were even more atrophic, weighing only 0.444 gm. Histologically, complete inhibition of spermatogenesis accounted for the marked loss of weight. The more pronounced atrophy in the treated groups was probably due to the concomitant interstitial cell atrophy caused by testosterone. In the cryptorchid groups, the abdominal testis averaged 0.372 gm. for uninjected animals and 0.246 gm. for the injected. Here again the greater atrophy in the case of injected animals was presumably due to interstitial cell atrophy. Our material confirms the almost generally accepted rule that destruction of spermatogenic cells, by agents such as Roentgen rays or cryptorchidism, goes hand in hand with an increased development of interstitial cells. The atrophy of the Leydig cells caused by testosterone is probably due to the fact that this steroid inhibits the gonadotropic hormone secretion of the hypophysis. We also noted that the seminal vesicles and prostates did not respond as well to testosterone in the irradiated animals as in the cryptorchid (1.034 gm. compared with 1.285 gm. for seminal vesicles, and 0.721 gm. compared with 0.823 gm. for prostates). This should be emphasized in view of the fact that the action of testosterone on these accessory sex organs is evidently direct. Thus the observations support the conception that Roentgen ray treatment may inhibit the direct actions of androgens. This series of experiments appeared to indicate that the direct stimulating effect of testosterone on the testis is ineffective after direct damage to the gonad. The following experiment was performed to test the possibility that this irresponsiveness of the testis might not develop if no time was allowed between intervention and treatment to permit gonadal atrophy to occur.

Experiment 2: Groups comparable to those of the first experiment having an average body weight of 58 gm. were treated during 21 days in the same way as above, except that injections of testosterone in the appropriate groups began on the day following the interventions. On the 23d day of the experiment, the animals were sacrificed and the organs taken for weight and histologic study. Table 2 summarizes the data.

TABLE 2.—EFFECT OF IMMEDIATE TESTOSTERONE TREATMENT ON TESTES DAMAGED BY ROENTGEN RAYS OR CRYPTORCHIDISM.

Treatment.	Testes wt. (gm.).	Sem. ves.	Prostate (mg.).
Untreated	1.382	56 mg.	132
Irradiated	0.547	34 mg.	116
Irradiated plus testosterone	0.484	574 mg.	419
Cryptorchid	0.556	39 mg.	102
Cryptorchid plus testosterone	0.615	1.019 gm.	634

Again both irradiation and cryptorchidism significantly reduced the testis weight, while injection apparently was ineffective in offsetting this atrophy. The fact that testosterone stimulated the

accessory sex glands far less effectively in the irradiated than in the cryptorchid group (0.574 gm. compared to 1.019 gm. for seminal vesicles, and 0.419 gm. compared to 0.634 gm. for the prostate) is even more striking than in the previous series.

It appears from these observations that if the testis is directly damaged, by transposition into the abdomen or exposure to Roentgen rays, it cannot be stimulated by testosterone whether treatment is initiated immediately following, or some time after the testicular damage. This insensitivity to the direct stimulating action of testosterone is in striking contrast with the obvious beneficial effects obtained by androgens in the previously quoted experiments in which testicular atrophy was induced by agents which presumably suppress the gonadotropic hormone production of the pituitary.

To complete our study of the hormonal therapy of testicular atrophy further experiments were performed on hypophysectomized animals. The literature on the action of steroid hormones on the testes of hypophysectomized animals has been discussed in previous publications[2,5] and is therefore omitted here. Suffice it to say that testosterone is capable of inhibiting the testis atrophy caused by ablation of the hypophysis. This stimulating action is therefore obviously not mediated by the pituitary gland. The interstitial cells, on the other hand, are not stimulated by testosterone after hypophysectomy, and actually undergo atrophy under the influence of this hormone in the intact animal. It appeared of interest to establish whether the interstitial cell inhibiting action of the hormone is likewise direct or whether it is merely due to inhibition of gonadotropic hormone secretion by the hypophysis. In order to establish this point, further experiments had to be performed in hypophysectomized males in which the interstitial cells were maintained in a well-developed condition by daily treatment with gonadotropic preparations. If the inhibitory action of testosterone were direct, it should be evident in the Leydig cells of animals thus treated,

---

LEGENDS FOR FIGS. 1 TO 6.

FIG. 1.—Testis of hypophysectomized untreated rat showing inhibition of spermatogenesis and atrophy of the interstitial cells.

FIG. 2.—Testis of hypophysectomized rat treated with L.H. Note inhibition of spermatogenesis and the numerous large interstitial cells.

FIG. 3.—Testis of hypophysectomized rat treated with L.H. and testosterone. Note partial restoration of spermatogenic activity. The interstitial cells are large and numerous as in Figure 2.

FIG. 4.—Testis of hypophysectomized rat treated with testosterone. Note partial restoration of spermatogenesis and atrophy of interstitial cells.

FIG. 5.—Testis of hypophysectomized rat treated with F.S.H. Note almost full range of spermatogenesis. Simultaneous development of interstitial cells may be due to traces of L.H. in the extract used.

FIG. 6.—Testis of hypophysectomized rat treated with F.S.H. and testosterone, showing almost full restoration of spermatogenic activity and moderately developed interstitial cells.

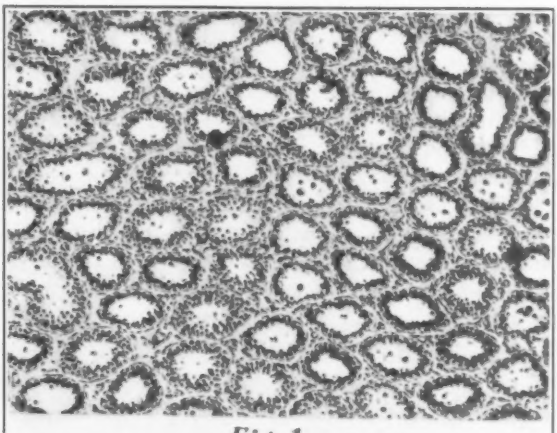


Fig. 1

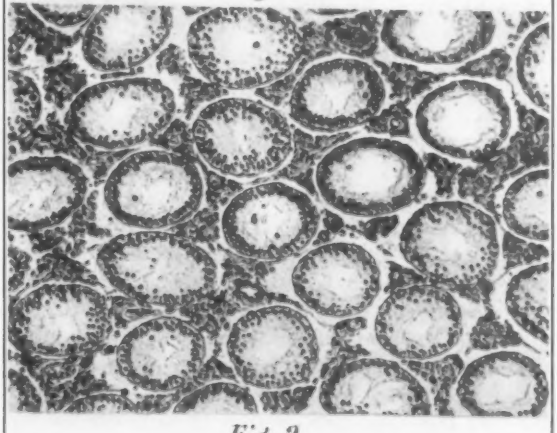


Fig. 2

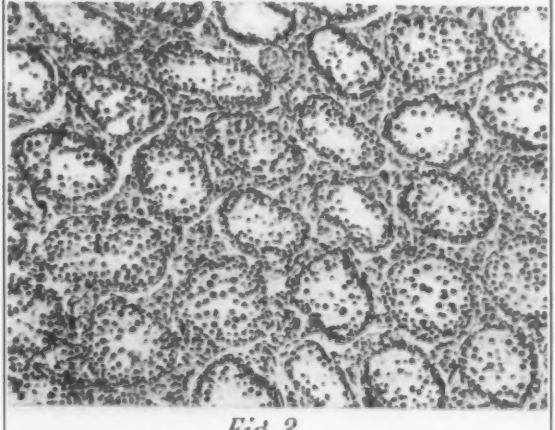


Fig. 3

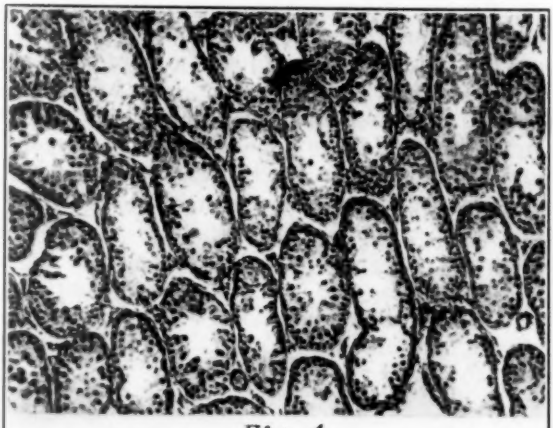


Fig. 4

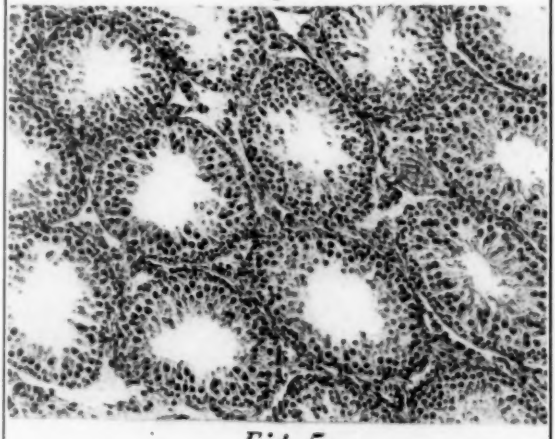


Fig. 5

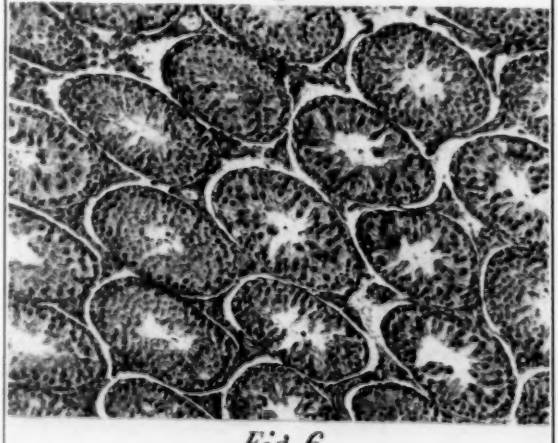


Fig. 6

but if it were due to a decrease of the normal gonadotropic hormone secretion of the pituitary, no effect could be expected in hypophysectomized rats receiving gonadotropic hormone by injection. In this connection, it is of interest that in female hypophysectomized rats estrogens do not cause the development of the large corpora lutea usually formed under the influence of such compounds in the intact animal. On the other hand, if the estrogens are given to hypophysectomized rats in combination with gonadotropic extracts, large corpora lutea are readily formed. This proved a peripheral synergism between gonadotropic hormones and estrogens in the female.[4] In view of these findings, it appeared important to establish whether a similar coöperation exists between the androgens and the gonadotropic hormones in the male. The following experiment was performed to clarify these points.

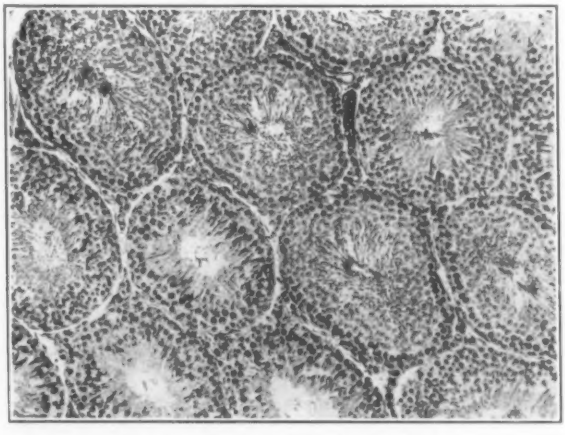


FIG. 7.—Testis of normal control rat.

Experiment 3: Seven groups of 6 male albino rats each with an average body weight of 86 gm. were treated as follows: Group 1, intact controls treated with oil; Group 2, hypophysectomized controls, treated with oil; Group 3, hypophysectomized treated with a luteinizing hormone (L. H.*); Group 4, hypophysectomized treated with L.H. and testosterone; Group 5, hypophysectomized treated with testosterone; Group 6, hypophysectomized treated with a follicle stimulating hormone (F.S.H.*); Group 7, hypophysectomized treated with F.S.H. and testosterone. The former was administered in doses of 100, the latter in doses of 50 I.U. in aqueous solution subcutaneously once daily. Testosterone was given sub-

* "A.P.L.," a purified pregnancy urine preparation made by Ayerst, McKenna and Harrison, Ltd., Montreal, was used as a source of L.H., and "Antex," a pregnant mare serum preparation made by Løvens Kemiske Fabrik, Copenhagen, was employed as a source of F.S.H.

cutaneously once daily in doses of 10 mg. in 0.4 cc. of peanut oil. A period of 14 days was allowed to elapse between the hypophysectomy and the initiation of treatment in order to permit severe testis involution, the animals were then treated for 14 days and sacrificed on the 29th day after hypophysectomy. In the course of the experiment, 3 animals in Group 4 and 2 in Group 7 succumbed. The gross weight of the testes of these animals which has been mentioned in another connection for comparative purposes[3c] is given in Table 3 together with the most outstanding histologic changes observed. Characteristic sections of the gonads of each group are illustrated in Figures 1 to 7.

TABLE 3.—EFFECT OF SIMULTANEOUS TREATMENT WITH TESTOSTERONE AND GONADOTROPIC HORMONES ON TESTES AFTER HYPOPHYSECTOMY.

Treatment.	Testes wt. (gm.).	Histology.
Normal controls	2.257	Normal
Hypophysectomy controls	0.164	Marked atrophy of germinal epithelium and Leydig cells
Hypophysectomy plus L.H.	0.532	Marked atrophy of germinal epithelium, stimulation of Leydig cells
Hypophysectomy plus L.H. and testosterone	0.607	Moderate atrophy of germinal epithelium, stimulation of Leydig cells
Hypophysectomy plus testosterone	0.394	Slight restoration of spermatogenesis, atrophic Leydig cells
Hypophysectomy plus F.S.H.	1.040	Normal spermatogenesis, large Leydig cells
Hypophysectomy plus F.S.H. and testosterone	0.960	Normal spermatogenesis, large Leydig cells

From these data, it appears that L.H. stimulates only the interstitial cells. This action may explain the slight increase in gross weight. F.S.H. stimulates the germinal epithelium as shown by the restoration of spermatogenic activity and consequently there is a significant increase in weight. The fact that this F.S.H. preparation also caused slight stimulation of the Leydig cells should probably be ascribed to traces of L.H. which may have been present in the commercial extract used. Testosterone stimulates the germinal epithelium and thus also causes partial restoration of weight but fails to influence the interstitial cell. Testosterone in combination with L.H. did not prevent the Leydig cell development caused by the latter, but synergized L.H., inasmuch as it induced considerable development of spermatogenic cells which was not seen in rats receiving L.H. alone. In the group injected with F.S.H. and testosterone, the Leydig cells were also well developed.

From these observations, we may conclude that the inhibitory action of testosterone on the Leydig cells is indirect and due to a decrease in the rate of gonadotropic hormone secretion.

Summary. In the rat, large doses of testosterone—which suffice to inhibit the testis atrophy produced by hypophysectomy, or agents which depress the gonadotropic hormone secretion of the pituitary—cannot counteract the testis involution due to direct

damage to the gonad by interventions such as Roentgen ray treatment or cryptorchidism. It appears that the latter agents render the testis insensitive to the stimulating action of androgens. The seminal vesicles and prostate likewise become relatively insensitive to testosterone following direct Roentgen ray treatment.

In hypophysectomized rats, gonadotropic pregnancy urine extracts stimulate only the interstitial cells but have little or no effect on the spermatogenic epithelium. When given in combination with large doses of testosterone, the luteinizing hormone of pregnancy urine retains its interstitial cell stimulating action. This indicates that the interstitial cell atrophy produced by similar doses of testosterone in intact animals is not due to a direct effect on these cells themselves, but probably to an inhibition of the gonadotropic hormone production by the pituitary. In the case of simultaneous administration of luteinizing hormone and testosterone, a synergism is noticeable, inasmuch as the interstitial cell development caused by the former is added to the germinal epithelium stimulating action of the latter. In experiments in which a pregnant mare serum preparation was administered to hypophysectomized rats both the spermatogenic epithelium and the interstitial cells showed signs of stimulation and neither of these effects was significantly modified by large doses of testosterone. There appears to be no marked synergism between the germinal epithelium stimulating action of pregnant mare serum preparations and testosterone.

The authors are especially indebted to Drs. Gregory Stragnell and Erwin Schwenk of the Schering Corporation for the testosterone, and to Dr. Stanley Cook of Ayerst, McKenna and Harrison, Ltd., of Montreal for the A.P.L. used in these experiments.

REFERENCES.

(1.) **Ferroux, R., Regaud, C.,** and **Samssonow, N.**: Compt. rend. Soc. de biol., **128**, 170, 1938. (2.) **Nelson, W. O.**: Anat. Rec., (Suppl.), **67**, 36, 1937. (3.) **Selye, H.**: (*a*) Canad. Med. Assn. J., **42**, 113, 1940; (*b*) Proc. Soc. Exp. Biol. and Med., 46, 142, 1941; (*c*) J. Urol, (in press), 1941. (4.) **Selye, H.,** and **Collip, J. B.**: Endocrinology, **20**, 667, 1936. (5.) **Selye, H.,** and **Friedman, S. M.**: Ibid., **28**, 129, 1941.

BOOK REVIEWS AND NOTICES

PHYSIOLOGY OF THE FETUS. Origin and Extent of Function in Prenatal Life. By WILLIAM FREDERICK WINDLE, Professor of Microscopic Anatomy, Northwestern University Medical School. Pp. 249; 70 illustrations, and 27 tables. Philadelphia: W. B. Saunders Company, 1940. Price, $4.50.

THE increasing interest in fetal and neonatal morbidity and mortality in obstetric and pediatric circles makes this monograph particularly timely. The book should be especially useful to those in research fields, and it provides the means for supplementing courses in embryology with the functional aspects of development. Those interested in behavior problems of children may find here knowledge of prenatal physiology which is often germane to their investigation. The book is divided into 15 chapters, each of which discusses the physiology of a particular system. The author devotes four chapters to the nervous system, with a final chapter to fetal nutrition and metabolism.

The introduction takes up comparative fetal physiology with reference to the selection of experimental material to be used in different problems. The author stresses that in the physiology of the fetus one is dealing with two organisms maintaining mutual although often precarious relationships to one another. In the discussion of the fetal heart he refers to the various clinical phenomena of interest to obstetricians, and sets out the theories which have been propounded to explain them. There is an excellent chapter on fetal circulation, including consideration of the mechanism which brings about the functional closure of the ductus arteriosus at birth.

In the discussion of the mechanism of fetal respiration the author leans to Henderson's theory of asphyxia at birth. The question as to whether or not the fetus normally aspirates amniotic fluid is answered.

The four excellent chapters on the physiology of the nervous system consider the genesis of function, fetal nervous activity and the eventual development of fetal motor reaction, reflexes, and fetal sense. Of particular interest today is the consideration of the fetal endocrine glands, in which the author states, *inter alia*, "we cannot be sure that fetal insulin plays any part in protecting the diabetic mother." A discussion of the various types of placenta, and comparative physiology of the nutrition and metabolism terminates the text. An appropriate bibliography is found appended to each chapter.

This critical interpretation and appraisal of many scattered observations on the physiology of the fetus should be of particular interest and value in research and clinical fields in which the problems of reproduction and fetal life are encountered. P. W.

TUMORES PRIMITIVOS MALIGNOS BRONCO-PULMONARES. Cancer, Sarcoma, Linfogranuloma. By JULIO PALACIO, Adjunct Professor of Clinical Medicine in the Medical Faculty of Buenos Aires; Director of the Municipal Dispensary for Respiratory Tract, and EGIDIO S. MAZZEI, Adjunct Professor of Medicine in the Medical Faculty of La Plata; Chief of Clinic in Professor Castex's Department; Chief of the Section on Human Pathology of the Research Institute. (Vol. III, Biblioteca Argentina de Medicina Interna.) Pp. 401; 129 illustrations and 4 colored plates. Buenos Aires: "El Ateneo," 1940.

THIS study of primary malignant tumors of the lung constitutes the third volume of a Biblioteca Argentina de Medicina Interna. It is based

on 120 cases observed in Professor Castex's clinic, the majority of which was confirmed at necropsy. Most of the work concerns "broncho-pulmonary cancer" (carcinoma) with shorter sections on sarcoma (various types) and lymphogranuloma (Hodgkin's disease). The various aspects of the subject are considered—incidence, etiology, pathology, diagnosis, prognosis, treatment—with especial emphasis on the radiologic study and on more than 20 clinically distinguishable sub-varieties. The book is well printed, well illustrated and contains a copious bibliography of 58 pages. It is a valuable contribution to a subject that is being actively investigated at the present time. E. K.

PATHOLOGICAL CONFERENCES HELD AT THE COOK COUNTY HOSPITAL BY DR. R. H. JAFFÉ. Edited by CHESTER C. GUY, M.D. Pp. 1164; 1 illustration. Chicago: Cook County Hospital Internes' Alumni Association, 1940. Price, $3.50. (For sale by Chicago Medical Book Company, (Chicago, Illinois.)

FOR nearly ten years the late Dr. Jaffé held weekly clinical-pathologic conferences at the Cook County Hospital in Chicago. These conferences were largely attended by staff and visitors, and probably were of particular value to the interns and residents. As a tribute and memorial to Dr. Jaffé, the Cook County Hospital Internes Alumni Association has collected notes on 596 conferences and made them available to a larger public. Each case report averages approximately two printed pages. The clinical notes are summarized by the attending physician, after which Dr. Jaffé tells of the lesions observed at the autopsy, pointing out features of interest, and discussing the pathogenesis of the lesions. The subjects selected cover a wide field. A good index adds much to the value of the book. This carefully prepared collection of case studies should prove of especial interest to those practitioners who are unable frequently to attend well-conducted post-mortem examinations. B. L.

THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE HEART. By HENRY A. CHRISTIAN, M.D., Sc.D. (Hon.), LL.D., F.A.C.P., Hon. F.R.C.P. (Can.), Hersey Professor of the Theory and Practice of Physic, Emeritus, Harvard University; Physician-in-Chief, Emeritus, Peter Bent Brigham Hospital, Boston, Mass. (Reprinted from Oxford Monographs on Diagnosis and Treatment.) Pp. 599; 28 figures. New York: Oxford University Press, 1940.

WRITTEN for the enlightenment of graduate physicians, this book presents the author's mature knowledge concerning the clinical diagnosis and the treatment of heart disease. According to the introduction: "This book is based in the main on the personal experience of the author obtained in the study of patients and their records at the Peter Bent Brigham Hospital, Boston, Mass., and in office and consultation practice . . . ." "So far as is possible, the correct diagnosis, anatomical, etiological and functional, is to be sought, and treatment is to be based on this diagnosis, in order that the best results are to be attained." W. J.

DISEASES AFFECTING THE VULVA. By ELIZABETH HUNT, B.A., M.D., CH.B. (Liverp.), Honorary Physician to the Skin Department, South London Hospital for Women; Honorary Dermatologist, New Sussex Hospital for Women and Children, Brighton, etc. Pp. 215; 36 illustrations and 18 plates in color. St. Louis: The C. V. Mosby Company, 1940. Price, $4.50.

THIS monograph, written from the standpoint of a dermatologist, is an excellent exposition of the subject and is beautifully illustrated. The 18 color plates lend to a more complete understanding of the subject. Some

of the plates show lesions of the oral mucous membranes side by side with similar lesions of the vulva and vagina. The author has described not only the usual skin disease but discusses thoroughly the neoplastic lesions found in this area, and has a series of excellent chapters on the vulvar manifestations of venereal diseases. The last chapter of the book is devoted entirely to vulvar conditions found in young children. The author concludes that kraurosis represents a late stage of leukoplakia and is thus opposed to the view that the two are distinct diseases.

The thorough consideration of all factors, especially hormonal influences, concerned with the diseases of this area and the very full sections on histopathology and treatment should make the book of especial value to the dermatologists and gynecologists. P. W.

THE EXTRA-OCULAR MUSCLES. A Clinical Study of Normal and Abnormal Ocular Motility. By LUTHER C. PETER, A.M., M.D., Sc.D., LL.D., Professor Emeritus of Diseases of the Eye in the Graduate School of Medicine of the University of Pennsylvania; Consulting Ophthalmologist in the Rush Hospital for Consumption and Allied Diseases, The Friends' Hospital for Nervous and Mental Diseases and the Roxborough Memorial Hospital. Pp. 368; 147 illustrations and 5 colored plates. Third Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $4.50.

THIS third edition of the author's well-known book on the extraocular muscles needs no introduction to those who specialize in ophthalmology. The author's clear concise style should appeal to all graduate students in this specialty. The chapter on nystagmus was written in collaboration with Dr. J. C. Yaskin and exemplifies his characteristic concise didactic teaching.

This book is to be recommended as a text for all those who propose to take up the study of ophthalmology. F. A.

DISEASES OF THE DIGESTIVE SYSTEM. Edited by SIDNEY A. PORTIS, B.S., M.D., F.A.C.P., Associate Clinical Professor of Medicine, Rush Medical College of the University of Chicago; Attending Physician, Michael Reese Hospital; Consulting Physician, Cook County Hospital, Chicago. (Fifty Contributors.) Pp. 952; 176 illustrations. Philadelphia: Lea & Febiger, 1941. Price, $10.00.

THIS book constitutes the first comprehensive presentation, in a single volume, of the entire field of gastro-enterology, including the diseases of the liver and the pancreas. Not only are the anatomy, the physiology and the organic and functional disturbances of the digestive tract fully covered, but also the gastro-intestinal aspects of those diseases that primarily affect other systems of the body. In addition the endocrinologic, the allergic, and, to a limited extent, the vitamin deficiency factors which enter into the production of digestive tract disease are clearly outlined.

In the preparation of the book Dr. Portis, as editor, has secured the assistance of 50 collaborating physicians. Each of them has been chosen because of his ability to make an authoritative presentation in his special field of interest. This, of course, has led to some repetition and inconsistencies, but on the whole the work may be regarded as an able presentation of the current opinions on the subject of gastro-enterology. In most instances when argumentative points are discussed ample references to the original literature are made.

The arrangement of the text is satisfactory, and the illustrations, with the possible exception of those on the intestinal parasites, are excellent.

Dr. Portis is to be congratulated on the production of a book for which there has been a long felt need, not only by the medical student but also by the general practitioner. V. M.

MEDIZIN UND KULTUR. Gesammelte Aufsätze von Paul Diepgen. Edited by W. ARTLETT, E. HEISCHKEL, and J. SCHUSTER. Pp. 309. Price, Paper, Rm. 21; Bound, Rm. 22.80. DAS PHYSIKALISCHE DENKEN IN DER GESCHICHTE DER MEDIZIN. By PROF. DR. MED. ET PHIL. DR. H. C. PAUL DIEPGEN. Pp. 39. Price, Rm. 2. Stuttgart: Ferdinand Enke, 1938 and 1939.

THESE medico-historic essays are from the pen of the Director of the Berlin Institute of the History of Medicine. "Medizin und Kultur" contains more than a score of Diepgen's articles, prepared between 1910 and 1936. It was produced for his 60th birthday on November 24, 1938. The selections illustrate his special interest in the practical significance of medical history; in historiography, folk medicine, medieval medical history, the history of gynecology, and so on.

Most of these essays were composed in calmer times, times more auspicious for historic study. The seven (or eight?) that were first published since the advent of Hitlerism, naturally have more than an average interest for Anglo-Saxon readers. One wonders, for instance, whether the occurrence in the same article of two such statements as: "It is no accident that the ever strengthening democratic and liberal thought among Europeans occurred in the period of modern biology and the theory of evolution" and "it is the totalitarian consideration of medicine that German National Socialism demands of him" (*i. e.*, the good physician), indicates a conflict in the writer's mind between conviction and expediency, or whether the point of view of German thought has so changed that such statements now assume a logical sequence for the author. In the earlier essays, the author frequently evinces his appreciation of the truly democratic in medical and civic progress. Let us hope that he may live to see truly democratic principles reëstablished in his Fatherland! In the meantime, what can be expected from a German university professor, when he is told by the Minister of Justice, as Raymond Fosdick quotes, that he "must ask himself one question: does my scientific work serve the welfare of National Socialism?" E. K.

STUDIES ON TUBERCULOSIS. The Spread of Tuberculosis in Negro Families of Jamaica, B.W.I. By E. JOYCE SAWARD, PERSIS PUTNAM, and EUGENE L. OPIE. The Fate of Negro Persons of a Tropical Country, Jamaica, B.W.I., after Contact with Tuberculosis. By EUGENE L. OPIE, PERSIS PUTNAM, and E. JOYCE SAWARD. A Survey of Tuberculous Infection in a Rural Area of East Alabama. By A. W. GRAHAM, P. W. AUSTON, and PERSIS PUTNAM. The Fate of Persons Exposed to Tuberculosis in White and Negro Families in a Rural Area of East Alabama. By A. H. GRAHAM, P. W. AUSTON, and PERSIS PUTNAM. Pp. 198; illustrated. Baltimore: The Johns Hopkins Press, 1941. Price, $1.10.

THIS monograph is composed of four articles reprinted from a recent number of the *American Journal of Hygiene*. It deals with two continuing investigations, supported by the Rockefeller Foundation, on the epidemiology of tuberculosis, with special reference to the spread of this disease in the Negro race. The studies reported, as is well known, represent outstanding work in this field, in which experts in pathology, clinical diagnosis, epidemiology and statistical treatment of data have combined in the analysis of data collected over a period of many years under conditions well suited to provide significant information. In general, the results call attention to the vital importance of environment in the spread of Negro tuberculosis and furnish strong support to the view that tuberculosis of the reinfection type in adolescents and adults is exogenous rather than endogenous. Within the monograph the results previously secured by the authors and their colleagues are incorporated, so that the volume, in its compact form, is a convenient source book for the study as a whole. E. L.

PHYSICAL CHEMISTRY FOR STUDENTS OF BIOLOGY AND MEDICINE. By DAVID INGERSOLL HITCHCOCK, PH.D., Associate Professor of Physiology in the Yale University School of Medicine. Pp. 264; 22 illustrations. Third Edition (with laboratory experiments). Springfield, Ill.: Charles C Thomas, 1940. Price, $3.50.

WE welcome a new edition of this well written and interesting textbook on the laws of dilute solutions. These solutions constitute for the medical student the most important part of physical chemistry. Useful features are the problems to be worked out by the student, and directions for a series of 20 laboratory experiments. For the physician who wishes to brush up on physical chemistry, the chapters on hydrogen ions, colloids, equilibria in blood, and enzyme action are especially useful, and knowledge of higher mathematics is not required. For the present edition much of the material has been rewritten. M. McC.

NEW BOOKS.

A History of Medicine. By ARTURO CASTIGLIONI, M.D., Formerly Professor at the University of Padua; Research Associate in the History of Medicine at Yale University. Translated from the Italian and Edited by E. B. KRUMBHAAR, M.D., PH.D., Honorary President of the American Association of the History of Medicine. Pp. 1053; 443 illustrations. New York: Alfred A. Knopf, 1941. Price, $8.50.

The Pharmacological Basis of Therapeutics. A Textbook of Pharmacology, Toxicology and Therapeutics for Physicians and Medical Students. By LOUIS GOODMAN, M.A., M.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine, and ALFRED GILMAN, PH.D., Assistant Professor of Pharmacology and Toxicology, Yale University School of Medicine. Pp. 1383; 126 illustrations. New York: The Macmillan Company, 1941. Price, $12.50.

Physical Medicine. The Employment of Physical Agents for Diagnosis and Therapy. By FRANK H. KRUSEN, M.D., F.A.C.P., Associate Professor of Physical Medicine, The Mayo Foundation, University of Minnesota; Head of the Section on Physical Therapy, The Mayo Clinic, etc. Pp. 846; 351 illustrations. Philadelphia: W. B. Saunders Company, 1941. Price, $10.00.

The Conducting Properties of the Human Organism to Alternating Current. By THOMAS ROSENDAL. Pp. 195; 68 figures and 42 tables. Copenhagen: Einar Munksgaard, 1940. Price, Dan. Kr., 15.

Techniques of Conception Control. By ROBERT LATOU DICKINSON, M.D., Former President, American Gynecological Society, and WOODBRIDGE EDWARDS MORRIS, M.D., General Medical Director, Birth Control Federation of America. Pp. 56; 50 illustrations. Baltimore: The Williams & Wilkins Company, 1941. Price, 50c.

Examination Questions in Laboratory Methods. Pp. 134: Bacteriology, 34; Clinical Pathology, 24; Blood Chemistry, 7; Hematology, 40; Tissue, 3; Basal Metabolism, 1; Parasitology, 6; Serology, 8; Miscellaneous Medical Subjects, 11. Compiled and published by The Gradwohl School of Laboratory Technique, St. Louis, Mo., 1941.

Milk Sickness Caused by White Snakeroot. By EDWIN LINCOLN MOSELEY, Professor Emeritus of Biology, State University, Bowling Green, Ohio; Past-President of Ohio Academy of Science. Pp. 171 (lithoprinted); 3 illustrations. Bowling Green, Ohio: The Ohio Academy of Science and The Author. Price, $1.00.

A monograph by a layman on an intoxication produced in cattle by eating a weed, white snakeroot, and in man usually by drinking the milk of poisoned animals. The disease, which has a high fatality rate in cattle and in man, and occurs in rural communities, especially in the Ohio Valley, was long a subject of controversy. The historical aspects of the monograph are therefore of particular interest.—R. K.

Cardiac Classics. A Collection of Classic Works on the Heart and Circulation with Comprehensive Biographic Accounts of the Authors. Fifty-two Contributions by Fifty-one Authors. By FREDRICK A. WILLIUS, M.D., M.S. in Medicine, Chief, Section of Cardiology, The Mayo Clinic; Professor of Medicine, The Mayo Foundation for Medical Education and Research, The Graduate School, The University of Minnesota, and THOMAS E. KEYS, A.B., M.A., Reference Librarian, The Mayo Clinic; Formerly Carnegie Fellow, The Graduate Library School, The University of Chicago. Pp. 858; illustrated. St. Louis: The C. V. Mosby Company, 1941. Price, $10.00.

"True Comics," Vol. 1, No. 1, a Bimonthly Magazine. DAVID T. MARKE, Editor. Pp. 17; illustrated. New York: The Parents' Institute, Inc., 1941. Price, 60c a year.

"Pediatricians and parents are increasingly concerned about the overstimulating effect of the increasingly lurid 'comic' magazines. . . . . As an antidote, the publishers of Parents' Magazine are launching a new magazine for boys and girls of all ages called 'True Comics,' similar only in format to the present 'comic' magazines. It differs radically in subject matter and editorial treatment." A number of pediatricians, psychologists and educators have already signified their approval of this interesting new venture in child psychology.—E. K.

The Heart in Pregnancy and the Childbearing Age. By BURTON E. HAMILTON, M.D., Cardiologist, since 1921, to The Boston Lying-In Hospital, Boston, and K. JEFFERSON THOMSON, M.D., Associate Physician, Metropolitan Life Insurance Company Sanatorium, Mt. McGregor, N. Y.; Research Associate in Medicine, Albany Medical College, etc. With a Section entitled "Delivery and Obstetrical After-Care of Cardiacs" by FREDERICK C. IRVING, M.D., F.A.C.S., Professor of Obstetrics, Harvard Medical School; Obstetrician-in-Chief, Boston Lying-In Hospital. Pp. 402; illustrated. Boston: Little, Brown & Co., 1941. Price, $5.00.

Pediatric Bibliography. By A. GRAEME MITCHELL, Department of Pediatrics of the College of Medicine, University of Cincinnati, and The Children's Hospital Research Foundation, Cincinnati. (Monographs of the Society for Research in Child Development, Vol. VI, No. 1 (Serial No. 27). Pp. 119 (lithoprinted). Washington, D. C.: Society for Research in Child Development, National Research Council, 1941. Price, 75c.

The Work of the Kidneys. A Guide for Use with the Instructional Sound Film "The Work of the Kidneys." Pp. 26; 6 illustrations. *Control of Body Temperature.* A guide for Use with the Instructional Sound Film "Control of Body Temperature." Pp. 25; 5 illustrations. Prepared by MELVIN BRODSHAUG, Erpi Classroom Films, Inc., and HELEN HAGGERTY, Hunter College, in Collaboration with A. J. CARLSON, H. G. SWANN and F. J. MULLIN, The University of Chicago. Chicago: The University of Chicago Press, 1941. Price, 15c each.

Medical Conferences of the University of Pennsylvania Bicentennial Celebration. *Hypertension* (M–8). By HARRY GOLDBLATT, EUGENE M. LANDIS, and ALFRED W. ADSON. (Pp. 46, Price, 50c.) *Cause and Growth of Cancer* (M–9). By LOUIS F. FIESER, STANLEY P. REIMANN, PEYTON ROUS, WARREN H. LEWIS, MARGARET R. LEWIS, and BALDUIN LUCKÉ. (Pp. 64; Price, 75c.) *Dental Caries* (M–11). By HENRY KLEIN, CARROLL E. PALMER, BASIL G. BIBBY, and ELMER V. MCCOLLUM. (Pp. 53; illustrated. Price, 50c.) *Problems of Intestinal Obstruction* (M–13). By JOHN P. PETERS, OWEN H. WANGENSTEEN, W. OSLER ABBOTT, ALLEN O. WHIPPLE, and JOHN A. NELSON. (Pp. 56; Price, 50c.) *The University and Public Health Statesmanship* (M **9,** 17). By ARTHUR P. HITCHENS, HARRY S. MUSTARD, WALLER S. LEATHERS, and CHARLES-EDWARD A. WINSLOW. (Pp. 33; Price, 50c.) Philadelphia: University of Pennsylvania Press, 1941.

Brucellosis (Undulant Fever). Clinical and Subclinical. By HAROLD J. HARRIS, M.D., Health Officer, Westport, N. Y.; Consulting Physician, St. Lawrence State Hospital; Attending Physician, Elizabethtown Community Hospital, etc. Foreword by WALTER M. SIMPSON, M.D., F.A.C.P., Director, Kettering Institute for Medical Research, Miami Valley Hospital, Dayton, Ohio. Pp. 286; 44 text and 12 colored illustrations. New York: Paul B. Hoeber, Inc., 1941. Price, $5.50.

The Story of Clinical Pulmonary Tuberculosis. By LAWRASON BROWN, M.D., Late Director of Trudeau Sanatorium; Lecturer in Trudeau School of Tuberculosis. Pp. 411; 1 illustration. Baltimore: The Williams & Wilkins Company, 1941. Price, $2.75.

Merchants in Medicine. By EMANUEL M. JOSEPHSON, M.D., Fellow, American Association for the Advancement of Science; American Academy of Ophthalmology and Otolaryngology, etc. Pp. 223. New York: Chedney Press, 1941. Price, $1.50.

The Medical Aspect of Boxing. By ERNST JOKL, M.D., Head of Department of Physical Education, Witwatersrand Technical College, Johannesburg, South Africa; Consultant, Medical Aspect of Physical Education, S. A. Defence Force. Pp. 251; illustrated. Pretoria, South Africa: J. L. Van Schaik, Ltd., 1941.

Essentials of Dermatology. By NORMAN TOBIAS, M.D., Senior Instructor in Dermatology, St. Louis University; Assistant Dermatologist, Firmin Desloge and St. Mary's Hospitals; Visiting Dermatologist, St. Louis City Sanitarium and Isolation Hospital. Pp. 407; 143 illustrations. Philadelphia: J. B. Lippincott Company, 1941. Price, $4.75.

Einführung in die Allgemeine chirurgische Diagnostik. By DR. G. DARDEL, Privat-Dozent für Chirurgie, Bern. Pp. 86. Bern: Hans Huber, 1941. Price, Fr. 6.80.

A Manual of Allergy for General Practitioners. By MILTON B. COHEN, M.D., Director of The Asthma, Hay Fever and Allergy Foundation; Visiting Physician in Allergy, St. Alexis Hospital, Cleveland. Pp. 156. New York: Paul B. Hoeber, Inc., 1941. Price, $2.00.

NEW EDITIONS.

The Pharmacology of Anesthetic Drugs. A Syllabus for Students and Clinicians. By JOHN ADRIANI, M.D., Instructor in Anesthesia, New York University College of Medicine; Assistant Visiting Anesthetist, Bellevue Hospital. Pp. 86; illustrated. Springfield, Ill.: Charles C Thomas, 1941. Price, $3.50.

Arthritis and Allied Conditions. By BERNARD I. COMROE, A.B., M.D., F.A.C.P., Instructor in Medicine, University of Pennsylvania; Senior Ward Physician, Hospital of the University of Pennsylvania. Pp. 878; 242 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1941. Price, $9.00.

Lectures on Diseases of Children. By SIR ROBERT HUTCHISON, BART., M.D., LL.D., F.R.C.P., Consulting Physician to the London Hospital and to the Hospital for Sick Children, Great Ormond Street, and ALAN MONCRIEFF, M.D., F.R.C.P., Physician to the Children's Department, Middlesex Hospital, and to Out-Patients, Hospital for Sick Children, Great Ormond Street; Pediatrician to Queen Charlotte's Maternity Hospital. Pp. 471; 107 illustrations. Eighth Edition. Baltimore: The Williams & Wilkins Company, 1940. Price, $6.75.

PROGRESS
OF
MEDICAL SCIENCE

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

JOSEPH C. BECK, M.D.,

ASSOCIATE PROFESSOR EMERITUS, DEPARTMENT OF OTO-LARYNGOLOGY, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE

AND

NOAH D. FABRICANT, M.D.,

ASSOCIATE, DEPARTMENT OF OTO-LARYNGOLOGY, UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE, CHICAGO, ILLINOIS.

MILITARY OTOLARYNGOLOGY.

A SIGNIFICANT trend can be detected in the content of many scientific journals. Since the fall of 1939 the march of military events has accented the surgical treatment of such basic problems as compound fractures, shell wounds, bullet injuries, blood transfusion—to mention but a few. Nor have the military aspects of oto-rhino-laryngology been overlooked. Though the American literature has treated the field but sparingly, it appears fairly certain that with a heightening of the world crisis an increasing number of articles will appear therein. Meanwhile, the American reader must rely mainly on reports from abroad.

Dickson and his associates[7] deal with the effects of airplane engine noise on the auditory acuity of aviators who have been subjected to it without protection for the ears. All observations were made with a pure tone audiometer. At first the loss is temporary, but it gradually becomes permanent. Deafness may not be noticed by the individual until the speech-hearing frequencies are involved. Bone and air conduction show a parallel loss. Though this loss is in the high tone range, wave analysis of aircraft noises shows that all the components of large amplitude are of low frequency. Thus it appears that a low tone noise is producing a high tone deafness. Protection of the ears diminishes the danger and different methods of protection are being tried. At present the flying helmet with close-fitting telephone receivers seems the most effective means of protection. In a discussion of gun fire deafness Passe[15] finds that naval personnel exposed to gun fire of 3, 4, and especially 4.7 inch caliber, if not operating in enclosed turrets, are subject to deafness. In more than half the cases observed, cotton-wool plugs were the only means adopted for protecting the ears. Deafness and tinnitus lasting for variable periods were complained of, and at times rupture of the tympanic membrane occurred. Though not always

complete, recovery invariably resulted, and the tinnitus subsided. The upper register in the audiofrequency scale was the last to recover. Craig[4] describes 6 cases of injury to the tympanic membrane caused in the present war by rifle fire, field gun fire, or bombing. None of the patients had worn any protectors and none had received any treatment until they arrived in the hospital, 1 to 9 days after the injury. Two of the cases seen within 24 hours did not develop otitis media and healed quickly; only 1 patient complained of pain, and that at the time of the explosion; no patient complained of giddiness. Wilhelm[20] finds that the ear is the organ most sensitive to the effects of vibrations and sudden variations of pressure, and consequently the most susceptible to sudden changes in the surrounding air. Such changes of pressure and degrees of intense noise are encountered by aviators, gunners, divers and the personnel of submarines. These differences of pressure and noise intensity are capable of producing tympanic and labyrinthine symptoms such as deafness, vomiting, disturbances of equilibrium and loss of consciousness. These at times are only transitory, but at others extremely dangerous. Campbell and Hargreaves[2] classify deafness of aviators according to the following causes: acute fatigue of the end organ of hearing and related structures; chronic accumulative fatigue of the end organ and related structures; conductive deafness due to changes in pressure in the middle ear; and chronic conductive deafness due to alteration in tissue resulting from faulty ventilation of the middle ear.

In the first World War 50% of those who died on the battlefield had been shot in the head or neck. Of the casualties passing through first-aid posts, 15% are head injuries, and by far their greatest risk is infection. According to Olivecrona,[14] partial or incomplete operative treatment of the wound does more harm than good. Early removal of foreign bodies and necrotic tissue is indicated, but it should not be attempted until the patient is in a hospital fully equipped for brain operations. Money[13] favors segregation of those with head injuries under the care of special teams. By as complete a removal of damaged tissues and foreign bodies as possible the prevention of sepsis can be hoped for with early operation. In penetrating injuries, if operation is delayed more than 24 hours, the death rate is much higher. Peiper[16] opposes operations on head injuries in or behind the front line. First-aid treatment should include removal of the hair and application of iodine to the scalp. To fix the bandage, two splints are applied, one from shoulder to shoulder, and the other from the middle of the back to the top of the head. The presence of neurologic signs is no indication for operation unless they are due to progressive compression. Otherwise the only indication for operation is to check infection. Splinters of bone are more likely to give rise to abscess than metal. Even the smallest wound on the scalp has to be carefully examined as early as possible. A severe depressed fracture may be hidden beneath a small wound, with or without injury to the brain.

Early local cleansing and loose suture of all facial wounds is advocated by Davis.[5] Wounds involving frontal sinuses and orbital and ethmoid regions are likely to be complicated by extensive fractures of the anterior fossa. This frequently leads to meningitis or intradural hemorrhage. Free drainage must be instituted very early. Bullet wounds through the antrum seldom need treatment. When the mandible is

fractured, teeth in the fracture line must be removed and fixation applied. Maxillo-facial injuries in war are described by James,[12] Axhausen,[1] Hautant[11] and Pichler.[17] The rôle of plastic surgery in injuries of the face is stressed by von Wedel[18] who maintains that repair of all soft tissue injuries should be early if possible, with thorough examination of injured parts, complete hemostasis, and accurate resuture of all layers. Thorough débridement under general anesthesia is essential in all wounds containing dirt. In facial fractures, other than jaw fractures, the first principle is never to remove any piece of bone; if it is loose, replace it and allow it to act as a bone graft. Replacement of fractured malar by the upper buccal sulcus route is advocated. The advantages of interdental wiring as a means of obtaining immediate immobilization of fractured mandibles is advanced by Walker.[19] The greatest utility is claimed for labial arch wiring. The advantages of this method are: where teeth are missing, the gaps can be bridged with the arch wire, traction can be applied in the right direction, and elastics can be used to effect a complete immobilization or a gradual reduction. This method is not advocated as a permanent fixation where there is a considerable loss of tissue. In commenting on war injuries of the jaws and face, Cole[3] believes that segregation of patients encourages specialized treatment and nursing while at the same time it has a beneficial psychologic effect on patients suffering from similar disabilities. The restoration of function is much more important than cosmetic considerations, and therefore the bony lesions should be dealt with first.

Wounds of the larynx are rare in modern warfare, not more than 3 per 1000 cases, but they are usually extremely serious when they do occur. In a large lesion of the laryngeal cavity first-aid consists in stopping hemorrhage and keeping the respiratory passages clear. Tracheotomy should always be carried out as soon as possible. Despons[6] emphasizes the importance of doing low tracheotomy under local anesthesia in injuries of the larynx, even when there is no open wound. Freud[9] calls attention to the effect on the voice of wounds of the lung and of the trachea, as well as of the larynx. Even when the vocal cords are injured it is possible by reëducative exercises to improve the voice, adapting the voice production and the breathing to the pathologic condition present. It is suggested that there should be special clinics for such individuals. According to Falk,[8] all injuries of the larynx should be regarded as surgical emergencies, and stretcher-bearers should be taught to prevent the wounded man from speaking. If dyspnea is a prominent symptom the patient should be carried with the head bent backwards, since this causes pressure of the larynx against the cervical spine and not only makes breathing easier, by widening the airway, but also helps to control bleeding by compression. In many cases it will be uncertain whether the esophagus is injured or not, and until this point is established, food and drink should be avoided, and the patient given rectal salines to prevent dehydration.

In view of its possible increased incidence in war time, Gissane and Rank[10] report a case of post-traumatic cerebrospinal rhinorrhea, successfully treated by operation. They conclude that a distinction between early and late onset of this condition is important with regard to prognosis and treatment. In the early type, which is apparent im-

mediately with severe head injuries, there is a tendency for spontaneous recovery if the patient survives the initial head injury. The delayed type occurs when the patient appears to have recovered from the initial head injury. For this group operation is indicated. In the case described by the authors a free graft of periosteum was placed over the roof of the frontal sinus to occlude the defect.

NOAH D. FABRICANT, M.D.

REFERENCES.

(1.) **Axhausen, G.**: Der Chirurg., **11**, 801, 1939. (2.) **Campbell, P. A.**, and **Hargreaves, J.**: Arch. Otolaryngol., **32**, 417, 1940. (3.) **Cole, P. P.**: Post-Graduate Med. J., **16**, 233, 1940. (4.) **Craig, D. H.**: Lancet, **2**, 40, 1940. (5.) **Davis, E. D. D.**: Brit. Med. J., **1**, 381, 1940. (6.) **Despons, J.**: Rev. de laryngol., Otol. and Rhinol., **60**, 733, 1939. (7.) **Dickson, E. D. D., Ewing, A. W. D.**, and **Littler, T. S.**: J. Laryngol. and Otol., **54**, 531, 1939. (8.) **Falk, P.**: Med. Welt., **14**, 81, 1940. (9.) **Freud, E.**: Ann. d'oto-laryngol., **1**, 14, 1940. (10.) **Gissane, W.**, and **Rank, B. K.**: Brit. J. Surg., **27**, 717, 1940. (11.) **Hautant, A.**: Ann. d'oto-laryngol., **3**, 169, 1940. (12.) **James, W. W.**: Brit. Dent. J., **68**, 125, 1940. (13.) **Money, R. A.**: Med. J. Australia, **1**, 443, 1940. (14.) **Olivecrona, H.**: Der Chirurg., **12**, 65, 1940. (15.) **Passe, E. R. G.**: Brit. Med. J., **2**, 295, 1940. (16.) **Peiper, H.**: Deutsch. med. Wchnschr., **65**, 1598, 1939. (17.) **Pichler, H.**: Wien. klin. Wchnschr., **53**, 22, 1940. (18.) **von-Wedel, C.**: South. Med. J., **32**, 1118, 1939. (19.) **Walker, D. G.**: Brit. Dent. J., **69**, 130, 1940. (20.) **Wilhelm, O.**: Bull. internat. serv. santé, **12**, 271, 1939.

NEUROLOGY AND PSYCHIATRY.

UNDER THE CHARGE OF

FRANKLIN G. EBAUGH, M.D.,

PROFESSOR OF PSYCHIATRY, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE, DENVER, COLO.,

AND

GEORGE S. JOHNSON, M.D.,

PROFESSOR OF PSYCHIATRY, STANFORD UNIVERSITY, SAN FRANCISCO, CALIF.

THE LITERATURE ON MILITARY PSYCHIATRY SINCE 1938.*

IN order to understand how psychiatry might help expected socio-economic disruptions, a fairly comprehensive survey was begun in 1938 of the available literature on the problems of psychiatry during the years 1914 to 1919 and on military psychiatry during subsequent years. In view of the events of the last 2 years, the author has attempted an interpretative review of the literature on Military Psychiatry.

The literature on military psychiatry since 1914, if sorted chronologically, falls easily into four periods, namely:

I: 1914 to 1919.
II: 1919 to 1929.
III: 1929 to 1938–39.
IV: 1938–39 to 1941.

* From the Psychiatric Liaison Department which is a division of the Department of Psychiatry of the University of Colorado School of Medicine and Hospitals, made possible by a Rockefeller Fund Grant.

PERIOD I (1914–1919). The literature of this period graphically depicts how psychiatry was then far less advanced than it is today and well isolated from the accepted fields of medicine, but well aware of the need to develop more of a genetic-dynamic understanding of mental ill-health and especially better therapeutic procedures. The literature shows how psychiatry arose to the demands of the armed services that their personnel be chosen more adequately in terms of personality competency, that steps be taken to preserve its mental health and to treat psychiatric casualties more effectually. The results of the labors of the few trained psychiatrists available at the time in surveying the situation, starting the education of the public in mental hygiene, formulating plans of procedure and following through those plans were truly amazing and productive. Psychiatry began to emerge from its isolation and gradually became recognized as an important branch of medicine. Mere custodial care of patients began to be replaced by active treatment and interest in research was stimulated.

PERIOD II. The literature on military psychiatry between 1919 to 1929 is characterized by reminiscences of the experiences of Period I, and lamentations that more could not have been done to prevent the staggering problem with which the country and medicine was faced in Period II in the form of psychiatrically disabled ex-service men. The literature of this era indicates furthermore that little, if any, specific planning was undertaken for a future emergency involving large numbers of psychiatric problems and shows a gradual diminution in any reference to military psychiatry, *per se*.

PERIOD III (1929 to 1938–39). The literature on military psychiatry during this interval is characterized by the absence of any significant writing on this specific subject, except occasional reports from the Veterans' Administration.

PERIOD IV (1938–39 to 1941). The literature of these years illustrates to some extent a repetition of the circumstances in which psychiatry found itself in the first period. Psychiatrists with far more knowledge of personality disorders, better techniques for diagnosis and improved therapeutic procedure, are now hurrying to formulate plans to meet the demands of the present crisis, realizing that a task of public education bigger than ever before lies ahead and that the need exists for long-term planning.

The general status, special problems and aspects of military psychiatry of the above first three periods and part of the fourth have been very adequately reviewed in Miller's recent book, "The Neuroses in War."[26] This book contains a comprehensive bibliography to the current literature of those times. Volume 10 (Neuropsychiatry) of "The Medical Department of the U. S. Army in the World War"[25] offers a very full account of the military psychiatric experiences of the U. S. Army during the first period. Since these books are available and practically no other writings of importance are to be found between 1929 and 1938, the remainder of this paper will be devoted essentially to a review of the current literature of the last 3 years dealing with military psychiatry. This will be done by arbitrarily grouping the material under several headings.

Incidence of Psychiatric Disorders—A Challenge. Many of the data dealing with the incidence of psychopathy among the personnel of the

armed forces during the last 3 years are but reiterations of those noted in earlier writings[25,26] on military psychiatry. They are noted here again for the purpose of orientation as to the magnitude of the problems now facing the medical profession.

In a recent paper Bowman[6] stated that one-half of the discharges from the English Army in 1917 were for neuropsychiatric conditions, and, excepting the actually wounded, one-third of all discharges were for personality disorders. Along this same line, this author points out that in the United States during World War I, 2% of the recruits and selectees were excluded from the Service, and, after induction, 3% more were discharged on account of neuropsychiatric disorders. It has been stated elsewhere[2] that in the United States in 1917, when few psychiatric facilities were available, 0.477% of the males of conscript age were rejected by draft boards because of "mental and nervous" difficulties.

According to Davidson,[13] 3% of those inducted into the U. S. Army in World War I were found to be "mentally defective." Of the soldiers sent to France, 3000 were found, after their arrival there, to be "imbeciles, paretics, epileptics and other types of psychopaths" and therefore not qualified for service. There were undoubtedly many more cases not apprehended. It has been estimated that 90% of the chronic war neuroses were discharged from the service undiagnosed and untreated.[20a]

Despite the many advances made in mental hygiene, psychiatric diagnosis, and in the psychiatric education of physicians, a great problem still faces us. In 1937, in a Naval Training Station in the United States, of 5578 recruits received for training over 1% were hospitalized before their training was completed for conditions which were existent before their enlistment and which were not aggravated by the naval service. Of this group of cases, over 45% were psychiatric disorders.[35] A statistical study[21] of several foreign units (Sweden, Belgium, Holland, Finland, Estonia, Poland, Germany) showed that 1% of all conscripts examined were rejected because of psychiatric conditions.

The problem does not consist merely in the maintenance of the efficiency of the armed forces at a given time. Social, economic and public health issues are also involved. Of the 54,117 ex-service men hospitalized by the Veterans' Administration,[1] approximately 60% were hospitalized because of neuropsychiatric disorders. Two out of every 5 veterans are receiving pensions because of neuropsychiatric conditions; and of every 5 veterans receiving compensation for service-connected disability, 1 is psychiatrically disabled by personality difficulties other than those accounted for by mental deficiency, psychopathic personality, chronic alcoholism, and paresis.[2] Since World War I, the Veterans' Administration is said to have spent one billion dollars[6] on claimants who have mental and nervous troubles stemming from their military services in World War I.

As of the last part of April, 1941, figures regarding the Selective Service rejections in the United States indicate that 6.2% were on account of "mental and nervous" disorders. This figure speaks well for the improved efficiency of American psychiatry in medical education and in rising to the present emergency to prevent some of the costly problems mentioned above. However, the unearthing of these cases

connotes an additional problem that must be met, namely, the follow-up guidance and treatment of these cases and the attempt at readjusting them more effectively to some useful form of civilian life.

The Psychopathology of Military Life. THE MAJOR PSYCHOSES. The literature of the past 3 years dealing with the psychopathology of military psychiatric casualties has to date given practically no space to the major psychoses other than to stress that the reactions are essentially the same as found in civilian life, that the treatment is likewise similar, and that all such cases should be eliminated from the service as soon as possible. The only exceptions to this trend noted by the author have been two papers, one dealing with depressive reactions and the other with very severe "support disorders."

Curran and Mallinson,[12] in a recent paper, point out that the evidence of "certifiable insanity" has not greatly increased in the Royal Navy as a result of war, but that the incidence of depressions in the Royal Navy personnel equalled that of hysteria (13% of psychiatric casualties). They suggest that the diagnosis of depression has been avoided because it connoted a major psychosis. The study of Curran and Mallinson was made on 44 cases which they felt presented primary mood disorders of the depressive type. These authors stated that depressive reactions were inclined to occur in "excellent men, who finally broke down, not through any deficiency in morale, but largely owing to certain deficiencies in adaptability due to a number of causes," such as: "age, temperament, quite a high proportion of mental backwardness or arteriosclerosis." Family history and domestic adversity seemed to be of little significance. The presence of hypochondriasis in the reactions was of little apparent prognostic importance. Most cases were said to have shown some hysterical coloring. Of all the cases, 28% were returned to duty, "26% showed on discharge any significant reduction in their previous social capacity and not more than 5 cases needed further hospital care." The average stay in hospital for these cases was 3 months. The percentage of officers returned to duty was high (a small series—8 out of 13). Good intelligence, personality plasticity, "rapid reactivity" and an illness lasting less than 6 months were favorable to a good prognosis. The early appearance of hysterical reactions tended to prolong the depressions and the more of this coloring the less likely the possibility of returning the patient to duty. Curran and Mallinson emphasize that the treatment of these depressive reactions is the same as in civilian life, that it is useless to attempt to "keep affective states in the firing line" and that in the treatment of these depressed "war cases," the "proportion of firmness to sympathy should vary in direct relation to the hysteria present."

In contrast to the psychiatric reactions that occurred in the British Army personnel not actively fighting in France (1939–1940) and who "would be expected to react according to their history of instability," Sargant and Slater[30] described a "new type" of reaction, an "acute neurosis" that appeared during the Battle of Dunkerque. These reactions, according to the authors, were inclined to occur in men who had previously shown a good work record, normal personality development and performance, satisfactory adjustment to army life, and were of normal intelligence. The soldiers on meeting such factors as bodily danger, continuous exertion, loss of sleep, inadequate food eaten irregu-

larly, intermittent but perpetual shelling, sight of comrades and civilians killed, and the continuous retreat without the possibility of retaliation, finally, after varying periods of time complained of "acute anxiety," insomnia or terrifying dreams when they did sleep, "inner unrest," and of being startled by noises. Objectively, these patients showed signs of exhaustion and appeared either tense and anxious or listless and apathetic. Their faces were immobile and this, along with the coarse, irregular tremor of the hands ("sometimes resembling that of an extrapyramidal lesion except in that the tremor could be controlled" momentarily) caused them, at first glance, to simulate the picture of Parkinsonism. In some there was nystagmus. These men were easily startled by noises, especially by those of airplanes, commonly showed an amnesia for the worst part of their experiences and manifested "many hysterical features such as confusion, fits, hallucinations," and so on. "With minimum treatment progress was towards improvement."

THE PSYCHONEUROSES. Lord Horder[17] was of the opinion that war produces no new type of personality disorders. He has outlined three classes of "neuroses": 1, "general concussion reactions" in men without visible wounds (5% to 10%); 2, "emotional shock" reactions (80% of cases) occurring either as "acute reactions in men with a predisposition" or slowly developing in others "as a result of prolonged strain and terrifying experiences often precipitated by some trivial experience; and 3, nervous and mental exhaustion as a result of prolonged strain and hardship." This authority states that in the "chronic cases of war neuroses" there exists a "congenital or acquired predisposition to excessive and therefore pathological reaction."

Hurst,[19] in an article in 1939, reviewed his experience with psychiatric disorders of World War I and compared them to those of civil life. He indicates that exhaustion and emotional strain are the two factors that account for a greater incidence of "neuroses" in men during wartime as compared with peace-time. Exhaustion, he points out, occurs in the setting of forced marching, strenuous fighting, and temperature changes. The added emotional strain occurs in the setting of bombardment, fighting, and conflict arising from participation in fighting. Hurst explains that these two factors lead to neurasthenic reactions that are more severe than those of civilian life, hysterical and obsessive-compulsive disorders, and also aggravate any incipient organic nervous system disease. The second or emotional factor, according to this clinician, may cause "functional hyperadrenalism and hyperthyroid states." "Terrifying experiences," he says "increase the susceptibility to suggestion, especially if physical injury occurs in association with the experience." In his paper, Hurst goes on to review some of the more common hysterical sequelæ to gassing, concussion, wounds, and so on.

In a recent article on aviation medicine, Ceres[10] indicates some of the psychiatric needs of aviation medicine. In his opinion, "fifty percent of the crashes in aviation can be attributed to the fault of the pilot—especially memory and attention difficulties and poor judgment." He discusses some of the psychiatric factors in high altitude and speed flying and, by implication, stresses the importance of evaluating the personality of aviators.

The Psychopathologic Effect of War on Civilian Populations. The first two works referred[25,26] to elucidate the very few available facts about civilian psychiatric reactions to warfare up to the summer of 1940. Since then the literature dealing with this subject has been scant. Since the summer of 1940, articles in languages other than English have been few and these smacked a little too much of propaganda and cautious writing on account of censorship to make evaluation by this author tenable. The English literature considering civilian reactions has as yet not brought out any new disorders as compared with World War I, and in the main indicates that about the same type of reactions have been precipitated in the two wars. So far as this author has been able to learn no factual statistics have been reported as to the number of civilian psychiatric casualties.

Adults. Stalker,[31] in June, 1940, indicated that at that time civilian panic states, marked enough to require hospital care, were few in number. He was inclined to believe that those that did arise occurred in people who were already psychiatrically sick. Boldie[4] has stated that, in the recent war, crimes of violence and even delinquency have diminished.

Pegge,[28a] in October, 1939, reviewed his experience with the psychiatric casualties that were admitted to his hospital during the first days of war. He reported a variety of conditions, not unlike the disorders of peace-time civilian life, that were precipitated by fear. According to Pegge, the fear of air raids that did not materialize constituted the chief strain, and in only a few cases did the air raid sirens act as the actual stimuli. The victims in general "were intelligent and of the educated classes."

One year later this same author [28b] analyzed the psychiatric casualties coming to the same institution from the civilian ranks. By this time most of the people had "become accustomed to air raid warnings and many psychiatric cases had been evacuated from the population." Of the 29 casualties studied, some were World War I "neurotics" who broke down under the strain of the times, but the majority were those who reacted psychopathologically when in actual danger or were knocked down by bomb blasts, and so on. Of the 29 cases, 13 gave no historical evidence of previous neurotic or psychotic tendencies. Five patients did give a history of previous personality difficulty and 2 "concussed" patients refused examination. He concluded that at least 17 of the 29 cases could be attributed to war stress. Most of these patients were hospitalized direct from bombed areas. They showed "varying degrees of disturbed consciousness—often amnesia." Coarse, generalized tremors, easily exaggerated by gun fire, were commonly shown by them. Besides, they often manifested "uncontrollable emotional behavior with weeping." Only 1 patient showed an hysterical reaction and "that was an old case" of hysteria.

Rosenburg and Guttman[29] have reported an interesting study made on 103 "chronic" psychiatric patients who had attended Maudsley Clinic for at least 1 year prior to September, 1939. They found that the patients with obsessive-compulsive reactions, the "chronic hysterias" and the hypochondriacs were relatively unaffected by the outbreak of the war, and subsequently needed no more attention than they had previously. On the other hand, the anxious and depressed

patients were adversely affected in that they tended to become more acutely ill.

The factors instrumental in bringing about psychiatric disorders in civilians exposed to the conditions of war have been variously listed by several authors.[4,5,26,27,32,37a,b,c] The following is a summary of these:

1. Fear due to:
   (*a*) Risk of attack or injury;
   (*b*) Economic change;
   (*c*) Threat of family separation;
   (*d*) Threat of food shortage;
   (*e*) Threat of deprivation of luxuries and pleasures.
2. Declination of individualism and increase in mass psychologic reactions such as anxiety.
3. Insufficient nutrition.
4. Inadequate rest.
5. Difficulty in maintaining social and personal hygiene.
6. Interference with occupational efficiency.
7. Evacuation to new surroundings.

CHILDREN. Although, as referred to above, one report[4] from England indicates that the incidence of delinquency among children has decreased since the outbreak of war, a review of the literature other than psychiatric and medical would seem to indicate that it probably has not done so, at least in the larger cities. The milder delinquency problems that in peace-time would be attended to are more or less trivial in war-time. Most of the papers dealing with the problems of childhood associated with the conditions of war in England indicate that "child neuroses" are greater in evacuees than those who remain at home with their parents.[4,14,34]

Other factors leading to behavior disorders in the children are: insecurity in a new environment, repercussion to adult strain, direct air raid experience, foster parents ignorant in child management, change in schools, indiscriminate and inadequate billeting, and return of the mother to the former home leaving the child behind. From the literature it seems that the child showing a reaction to bombing is easily and successfully treated, while the one reacting to a broken home is very difficult to clear. One author[14] interestingly noted that over three-fourths of the children showing behavior disorders were between the ages of $7\frac{1}{2}$ and $11\frac{1}{2}$ years. The diagnostic and age incidence of the reactions ran practically the same as has been noted in the psychiatric referrals from a pediatric clinic in a large inland American hospital.[3b] It is felt, therefore, that the type of reaction and the age at which it occurs are not significant insofar as war is concerned. If the experiences of peace-time hold true, then this author feels that some of the later reactions of life stem from prolonged strain with anxiety and the adverse emotional tendencies, disturbed habits, and so on, in childhood. In view of this, it is more than a likelihood that more adult disorders can be expected in the future, especially if civilian populations continue to be subjected to the stresses of modern warfare for a long period of time.

Prevention. How to prevent even most of the psychiatric disorders of the personnel of the armed forces cannot be solved during a critical period such as now. A practical answer will be forthcoming if psychiatry and medical education in general do not lapse into as much of a state of inertia in regard to military and industrial medicine as they

did in 1919 to 1939, following World War I. Of course, too, in setting forth upon such a program, it probably is worth bearing in mind that it might not be practical to exclude all moderately unstable men from the service, since many of them, under certain exigencies have, are, and will continue to perform their duties with efficiency and valor.

Gordon[18] suggests that all physicians eventually should be given the means by which they can evaluate the strain to which a person is subjected and the amount of stress an individual can tolerate without "breaking" in order that prevention of psychopathic episodes can be augmented. Others,[7,11,13,17,24,33] in discussing prevention of personality disorders have made the following recommendations:

1. Every examining board physician and individual officer should have a knowledge of personality disorders and be encouraged to use it.
2. All recruits and selectees should be drafted for a period of probational training of 3 to 6 months, in order that the misfits, neurotics, psychopaths and psychotics can be eliminated.
3. Departments should be developed to form a liaison between school and community agencies and other services so that educational, social and health records of the recruits and selectees can be made more easily available in evaluating the men before induction.
4. Group psychometric tests should be done on all men before induction.
5. Armed services should, as far as it is feasible and possible, avail themselves of the experiences and techniques of industry in choosing personnel.
6. There should be one psychiatrist, or physician with some psychiatric knowledge on each county draft board—at least on each of the larger county draft boards.

Lord Horder[17] has advised that in order to prevent many of the psychiatric problems of war, the following should be instituted:

1. Education of the public (*a*) in the fundamentals of personality functioning and the disorders thereof; (*b*) in the realization that a "neurosis," no matter what the cause, is not to be considered a battle casualty and that psychiatric illness cannot, *per se*, be a basis for honorable discharge from the service.
2. More attention to eliminating poor sanitation, bad housing accommodations, and abuse of alcohol, drugs, and so on.
3. More attention to the dietary of the populace, especially of the soldier.
4. Control of venereal disease.
5. Elimination from medical and psychiatric terminology of such terms as "shell shock," disordered action of the heart (D. A. H.), neurocirculatory asthenia, and all others that implicate a part of the body as being diseased when it is only participating in a personality reaction.

Besides the foregoing, this author would like to suggest that the following additional preventive measures be considered:

(*a*) Instructing the public in mental health through a wider propagation of *facts* than now prevails and more attention to improving laws dealing with the mentally sick.

(*b*) Existing agencies should be made use of or new ones established to advise and assist rejectees in making better civilian adjustments and in obtaining medical and psychiatric treatment.

(*c*) Rehabilitation and vocational guidance services should be set up to reëstablish disabled and discharged service men in society in a useful way.

(*d*) Development of more or less permanent organizations to formulate means of improving case records, to evaluate the clinical and other data, to direct research and to integrate those data with new medico-psychiatric movements and projects that are of particular importance to both military and civil mental health.

(*e*) Future maintenance of interest and active work in the field of military, industrial and vocational psychiatry.

Prognosis. "The prognosis as to the recovery of a psychiatrically ill soldier or officer sufficient to permit his return to active service is, in

the light of present knowledge, rather difficult to evaluate since very few statistics are available. Certainly several factors are always operative and have to be considered in any such prognostication. These are: the age of the disabled soldier or officer, his intellectual level, his pre-army and pre-war social adjustment and behavior, the conditions under which the personality disorder developed, the nature and duration of the psychopathologic reaction and the circumstances under which treatment is administered.

"It goes without question that those individuals unable to adjust to army life and to function efficiently by the time the first half of the indoctrination period has passed, will never be able to do so, and, therefore should be eliminated from the service. If the need for man power is compelling and the local situation permits, many men of relatively low intelligence but of stable temperament, some with minimal psychopathic trends, a few "stationary" organics or those amenable to treatment, a few mildly depressed soldiers, and many of the psychoneurotics, frequently can be allocated duties that are either simple, or offer little strain and are within the capacity of the particular soldier. Discussion of the soldier's personal problems in terms of special considerations by medical and line officers will avert many actual breakdowns and will work toward increasing the morale and efficiency of the respective units.

"Experience in the World War I seems to indicate that once a soldier, in the service, develops a major psychosis, excepting a delirium, the chances are very poor for rehabilitating him sufficiently for return to active duty. The psychotic soldier should, therefore, be evacuated and as soon as feasible eliminated from the service.

"In the instance of psychoneurotic developments, especially during the pre-engagement and combat periods, prognosis is likewise variable. However, the psychiatric experiences of the World War I, and subsequently, indicate that the expected outcome of adequately treated psychoneurotic reaction types with onset in the combat zone will be about as follows:

Exhaustion and fatigue states Concussive reactions without central nervous system injury Hypermotility states "Gas neurosis" Conversion-hysterical states Anxiety states and "anticipation neuroses" Obsessive and compulsive reactions Hypochondriases Tension and irritable weakness reactions	Possibility of an officer or soldier returning to active duty decreasing from above downward

"It is estimated that about 25% to 30% of the psychiatrically disabled officers and approximately 55% to 65% of the privates and non-commissioned officers will be able to return to full active duty after a psychoneurotic episode.

"It is to be expected that the farther from the site of the inception of the disorders, especially the psychoneurotic ones, that treatment is instituted, the less the expectancy for recovery. This is particularly true during the combat period."[3a]

The prognosis is poor for returning an officer or soldier to full and active duty if he develops a psychoneurosis or psychosis while on furlough or "leave."

If a soldier is incapable of returning to active service, the facilities of the various social agencies should be utilized, when advisable, in steering him into some constructive work as a civilian.[3a,8,11,16,20b,22,23,25,26]

The average physician is often inclined to procrastinate about committing himself as to the essential negativity of organs that participate in the various psychopathologic states. As has been alluded to previously, the result is that the psychiatrically ill soldier is made too body conscious and thereby invalided. For this reason the British authorities[17] have advised against such practice. For example, Whishaw[39] studied 250 invalided ex-soldiers of World War I, 20 years after the onset of their disability. Of these men, 156 (62%) had carried the diagnosis of "D.A.H. or psychoneurosis" for 20 years; 130 of them had "D.A.H." Of these 130 men, 126 were found to have normal hearts in 1939. Two of the remaining 4 had developed hypertensive heart disease, 1 chronic nephritis and 1 rheumatic heart disease subsequent to their war service. Of these 130 ex-soldiers, 35% still considered themselves totally disabled and all were heart conscious.

Treatment. Even to summarize the treatment of the psychopathologic states of war-time would require space far beyond the limits of this paper. Miller[26] and Kardiner[20b] have done this exceedingly well in their respective texts. Since the therapy of war-time disorders is essentially that of peace-time, the standard texts on psychiatry can be referred to. The review to follow is based entirely on some of the more pertinent current literature, read by the author during the last 3 years.

The history of psychiatry in the World War I[25,33] proved that intelligent handling of psychiatric problems increased the percentage of recoveries, improved the morale of the forces and increased their general efficiency. Mayer-Gross[24] has outlined what war-time psychiatry should do to be of full service. The points he emphasized follow:

1. Making it possible for recruiting and medical officers to consult psychiatrists in all doubtful cases.
2. Psychiatric consultation should be available in all general and base hospitals.
3. Special psychiatric units of general hospitals or psychiatric hospitals should be easily available.
4. All acute "neuroses" should be treated in or as near as possible to the combat area.
5. As many as possible of the "neurotics" returned to the Zone of the Interior should be rehabilitated in civilian ranks.
6. All surgical cases "with non-penetrating or penetrating head wounds should be treated psychologically and educationally as well as surgically."
7. Civilian understanding of personality problems should be improved.

Several British psychiatrists,[15,30] basing their conclusions on therapeutic experiences with 1500 cases, state that "radical treatment is out of the question." They attempt to handle the patient's symptoms, improve his general health, and by history-taking and interviews with the patient under the influence of hypnotics use suggestion and desensitization to return him to his "pre-breakdown" condition. Their objective is to return the patient quickly to active duty, or to outline procedures for his readjustment to a socially valuable life. These authors point out that one of the difficulties in treating the military psychiatric casualty is to be found in what ultimate recovery may mean to the patient. In civilian life "the reward for getting well is greater freedom from hampering difficulties." In the military case,

"the reward is the privilege of returning to the scene of his failure with the knowledge that he has failed." Debenham and his confrères caution against the therapist being too optimistic and not "invaliding" casualties quickly enough.

As to the handling of "violent and suicidal patients," Weatherby[36] gives good advice, similar to that to be found in the standard textbooks on psychiatry.

In treating the civilian panic and confusion states, concurrent with the bombing of Britain, referred to previously under the heading of *psychopathology*, Pegge[28b] used the following procedure: The patient is seen and examined as soon as possible. If he is not conscious, he is treated as though hypnotized; that is, he is given reassurance specific to the use of disturbed functions, explanation is made of the mechanism of symptom formation, the patient is commanded to open his eyes and give his name and address. If the patient is excited and disoriented, he is given a hypnotic drug (after explanation) and suggestions are carried out as before. All cases are seen on the second day and the treatment procedure repeated. If the patient has not recovered in hospital within 3 days he is sent to a psychiatric hospital. Of the 29 cases reported, 6 were successfully treated in the out-patient clinic and 10 in the hospital within 3 days. Eleven were referred to psychiatric hospital, 1 was sent to a "psychiatric observation ward" and 1 refused treatment.

In a study of the anxiety of civilians concomitant with the "war of nerves" and the bombing of cities, one author[4] fears that if treatment is not efficient, there is possibility of many affected civilians developing "hiding and shelter habits," panics, compulsive disorders and "neurotic disabilities."

Cameron[9] emphasizes the value of occupational therapy in treating the psychiatric casualties of war. He advises that an occupational therapy department should be an integral part of every hospital and it should be under the direction and control of a medical officer. The work should naturally be useful and varied, prescribed specifically for the individual and should be regarded as treatment.

Conclusions. Perusal of the literature shown in the bibliography indicates that nearly all of the writers, besides reporting details of their experiences and techniques, have made a plea that psychiatry keep to the middle of the road, improve more rapidly the courses in psychiatry for medical students, develop facilities whereby all medical officers can have instruction in the principles of personality functioning and the diagnosis and treatment of the disorders thereof, give attention to improving compensation laws, stimulate the public to organize adequate facilities to readjust the rejectee, the discharged and invalided men of the services, present more facts to the public at large in regard to the disorders of personality, and correlate the researches of the many allied fields of science that have a bearing on psychiatric medicine.

EDWARD G. BILLINGS, M.D.
ASSOCIATE PROFESSOR OF PSYCHIATRY; DIRECTOR OF THE PSYCHIATRIC LIAISON DEPARTMENT, UNIVERSITY OF COLORADO SCHOOL OF MEDICINE AND HOSPITALS, DENVER, COLO.

REFERENCES.

(1.) Annual Report, Administration of Veterans' Affairs, Fiscal Year ended June 30, 1939, Washington, D. C., Govt. Print. Off., 1939. (2.) **Baganz, C. N.**: Mil. Surg., **86**, 471, 1940. (3.) **Billings, E. G.**: (*a*) For Subcommittee on Clin.. Psychiat.: "A Brochure for Medical Officers on the Recognition, Prevention and Treatment of Personality Disorders in Soldiers," March 14, 1941; (*b*) The Value of Psychiatry to the General Hospital (to be published). (4.) **Boldie, A.**: Brit. Med. J., **1**, 330, 1941. (5.) **Bonhöffer-Schjerning, O. K. W.**: Handb. d. Aerztl. Erf. im Welt, Leipzig, Barth, **4**, 1, 1922. (6.) **Bowman, K. M.**: War Med., **1**, 213, 1941. (7.) **Boyer, G. F.**: Canad. Med. Assn. J., **43**, 53, 1940. (8.) **Brown, W.**: Lancet, **2**, 197, 1918. (9.) **Cameron, K.**: Ibid., **2**, 659, 1940. (10.) **Ceres, F.**: War Med., **1**, 43, 1941. (11.) **Culpin, M.**: Lancet, **2**, 257, 1941. (12.) **Curran, D.**, and **Mallinson, W. P.**: Brit. Med. J., **1**, 305, 1941. (13.) **Davidson, H. A.**: Mil. Surg., **86**, 477, 1940. (14.) Debate at Tavistock Clinic: Lancet, **1**, 121, 1941. (15.) **Debenham, G.**, **Hill, D.**, **Sargant, W.**, and **Slater, E.**: Ibid., **1**, 107, 1941. (16.) **Dillon, F.**: Ibid., **1**, 57, 1919. (17.) Editorial: Brit. Med. J., **2**, 1199, 1939. (18.) **Gordon, R. G.**: Ibid., **1**, 120, 1940. (19.) **Hurst, A. F.**: Guy's Hosp. Rept., **89**, 423, 1939. (20.) **Kardiner, A.**: (*a*) War Med., **1**, 219, 1941; (*b*) Traumatic Neuroses of War, Psychosomatic Medicine, Monograph, II–III, Washington, Nat. Res. Coun., 1941. (21.) **Landis, C.**, and **Page, J.**: Magnitude of the Problem of Mental Disease, Mental Health (Symposium), Lancaster, Science Press, pp. 149–155, 1939. (22.) **Lee, R. A.**: Personal Relations in Industry, published by General Motors Corp. (23.) **Leigh, A. D.**: Lancet, **1**, 394, 1941. (24.) **Mayer-Gross, W.**: Ibid., **2**, 1327, 1939. (25.) Medical Department, U. S. Army in World War, vol. 10 (Neuropsychiatry), Washington, U. S. Govt. Print. Off., 1929. (26.) **Miller, E.**: The Neuroses in War, New York, The Macmillan Company, 1940. (27.) **Mira, E.**: Brit. Med. J., **1**, 1217, 1939. (28.) **Pegge, G.**: (*a*) Ibid., **2**, 764, 1939; (*b*) Ibid., **2**, 553, 1940. (29.) **Rosenburg, E. A.**, and **Guttman, E.**: Lancet, **2**, 95, 1940. (30.) **Sargant, W.**, and **Slater, E.**: Ibid., p. 1. (31.) **Stalker, H.**: Brit. Med. J., **1**, 887, 1940. (32.) **Stelzner, H.**: Arch. Psychiat. and Nervenkrankh., **55**, 365, 1915. (33.) **Sutton, D. B.**: U. S. Naval Bull., **37**, 262, 1939. (34.) Symposium: Proc. Roy. Soc. Med., **33**, 374, 1940. (35.) **Thomas, G. E.**: U. S. Nav. Med. Bull., **37**, 276, 1937. (36.) **Weatherby, F. E.**: Mil. Surg., **84**, 486, 1939. (37.) **Whittkower, E.**, and **Spillane, J. P.**: (*a*) Brit. Med. J., **1**, 223, 1940; (*b*) Ibid., p. 265; (*c*) Ibid., p. 308. (38.) **Willcox, P. H.**: Ibid., p. 1008. (39.) **Whishaw, R.**: Med. J. Australia, **2**, 891, 1939.

GENERAL BIBLIOGRAPHY.

1916.

Campbell, A. W.: Med. J. Australia, **1**, p. 319. **Mann, G.**: Wien. klin. Wchnschr., **29**, p. 1651. **Mann, L.**: Berl. klin. Wchnschr., **53**, p. 1053. **v. Nesnera, E.**: Wien. klin. Wchnschr., **20**, p. 1616. **Regis, E.**: Boston Med. and Surg. J., **175**, p. 784. **Tullidge, E. K.**: Penna. Med. J., **19**, p. 778.

1917.

Adler, J. M.: Ment. Hyg., **1**, p. 364. **Adrian, E. D.**, and **Yealland, L. R.**: Lancet, **1**, p. 857. **Auer, E. M.**: Ment. Hyg., **1**, p. 383. **Farrar, C. B.**: Am. J. Insan., **73**, p. 693. **Owen, F. E.**: J. Abnor. Psychol., **12**, p. 217. **Salmon, T. W.**: Mil. Surg., **41**, p. 674.

1918.

Bailey, P.: J. Am. Med. Assn., **71**, p. 2148. **Brock, A. J.**: Lancet, **1**, p. 436. **Collie, J.**: Ment. Hyg., **2**, p. 1. **Core, D. E.**: Boston Med. and Surg. J., **179**, p. 448. **Eager, R.**: Brit. Med. J., **1**, p. 422. **Farrar, C. B.**: Am. J. Med. Sci., **155**, p. 425; Boston Med. and Surg. J., **179**, pp. 583, 615. **de Fursac, J. R.**: Am. J. Insan., **75**, p. 19. **Hill, D. S.**: Ment. Hyg., **2**, p. 611. **Hunt, E. L.**: Med. Rec., **94**, p. 91. **Hyder, H. P.**: Ibid., **94**, p. 806. **Jelliffe, S. E.**, and **Payne, C. R.**: J. Nerv. and Ment. Dis., **48**, pp. 246, 325. **MacCurdy, J. T.**: War Neuroses, Cambridge University Press. **Mott, F. W.**: Lancet, **1**, pp. 127, 169. **Read, C. S.**: Ment. Hyg., **2**, p. 359. **Rivers, W. H. R.**: Lancet, **1**, p. 173; Ment. Hyg., **2**, p. 513. **Turner, W. A.**:

Lancet, **2**, p. 613. **White, E. W.**: Brit. Med. J., **1**, p. 421. **Wolfsohn, J. M.**: J. Am. Med. Assn., **70**, p. 303. **Yealland, L. R.**: Hysterical Disorders of Warfare, London, MacMillan & Co.

1919.

Abbot, E. S.: Am. J. Insan., **75**, p. 457. **Brownrigg, G. E.**: Boston Med. and Surg. J., **181**, p. 458. **Chambers, W. D.**: J. Ment. Sci., **65**, p. 152. **Gregory, N. S.**: Arch. Neurol. and Psychiat., **1**, p. 89. **Lind, J. E.**: Med. Rec., **96**, p. 7. **McPherson, G. E.**: Arch. Neurol. and Psychiat., **2**, p. 207; Boston Med. and Surg. J., **181**, p. 606. **Major, H. S.**: J. Missouri Med. Assn., **16**, p. 377. **Meagher, J. F. W.**: Am. J. Med. Sci., **158**, p. 344. **Pearn, O. P. N.**: J. Ment. Sci., **65**, p. 101. **Rhein, J. H. W.**: Am. J. Insan., **76**, p. 71; New York Med. J., **110**, p. 177. **Russel, C. K.**: Arch. Neurol. and Psychiat., **1**, p. 25. **Salmon, T. W.**: New York Med. J., **109**, p. 993. **Schwab, S. I.**: Arch. Neurol. and Psychiat., **1**, p. 579. **Smurthwaite, H.**: J. Laryng., Rhin. and Otol., **34**, p. 13. **Stewart, J. P.**: Arch. Neurol. and Psychiat., **1**, p. 14. **Walsh, J. J.**: Internat. Clin., **2**, p. 148.

1920.

Jones, E.: Treatment of the Neuroses, New York, William Wood & Co., Ch. 8, pp. 202–209. **Leahy, S. R.**: Arch. Neurol. and Psychiat., **4**, p. 191. **Salmon, T. W.**: Mil. Surg., **47**, p. 200. **Sheehan, R.**: Ibid., **47**, p. 295. **Stephenson, J. W.**: Arch. Neurol. and Psychiat., **3**, p. 61. **Taylor, E. C.**: U. S. Nav. Med. Bull., **14**, p. 191.

1921.

Benton, G. H.: J. Am. Med. Assn., **77**, p. 360. **Brown, S., Jr.**: Ibid., p. 133. **Herbert, S.**: Lancet, **1**, p. 1238. **Robinson, G. W.**: J. Missouri Med. Assn., **18**, p. 435. **Wolfe, S.**: Mil. Surg., **49**, p. 272.

1922.

Massonneau, G.: Ment. Hyg., **6**, p. 575. **May, J. V.**: Mental Diseases, Boston, Richard G. Badger, Ch. 11, pp. 185–201. **Thom, D. A.**, and **Singer, H. D.**: Ment. Hyg., **6**, p. 23. **Trentzsch, P. J.**: Med. Rec., **101**, p. 369.

1923.

Farrar, C. B.: Am. J. Psychiat., **2**, p. 665. **Heldt, T. J.**: Ibid., **2**, p. 647. **Ireland, G. O.**: Ibid., p. 6875. **Somerville, H.**: J. Ment. Sci., **69**, p. 170.

1929.

Medical Dept. U. S. Army in the World War, vol. **10**, Neuropsychiatry, Washington, U. S. Govt. Print. Off.

1937.

Deutsch, A.: The Mentally Ill in America, Garden City, Doubleday, Doran & Co., Inc., Ch. 15, pp. 317–318.

1939.

Carlson, W. A.: J. Aviation Med., **10**, p. 216. **Dillon, F.**: Brit. Med. J., **2**, p. 63, **Hamlin, P. G.**: J. Aviation Med., **10**, p. 129. **Russel, C. K.**: Canad. Med. Assn. J., **41**, p. 549. **Snowden, E. N.**: Lancet, **2**, p. 1130. **Sullivan, H. S.**: U. S. Nav. Med. Bull., **37**, p. 273. **Weber, F. W. A.**: Münch. med. Wchnschr., **86**, p. 1305.

1940.

Armstrong, H. G.: Ann. Int. Med., **13**, p. 2212. **Darnell, J. R.**: J. Am. Med. Assn., **115**, p. 1443. Effort Syndrome (Committee report explaining symptom and diagnostic tests), Brit. Med. J., **2**, p. 201. **Hillman, C. C.**: Ann. Int. Med., **13**, p. 2205. **Hurst, A.**: Medical Diseases of the War, Baltimore, The Williams & Wilkins Company. **Minty, C. C.**: Med. J. Australia, **2**, p. 386. **Parkinson, C. K.**: Ibid., **1**, p. 94. Psychiatry and the National Defense, Psychiatry, **3**, p. 619. **Sutton, D. G.**: Am. J. Psych., **97**, p. 255.

1941.

Baillie, W.: Am. J. Psych., **97**, p. 753. **Brown, E. W.**: War Med., **1**, p. 1. **Campbell, C. M.**: J. Am. Med. Assn., **116**, p. 1883. **Cohen, S. A.**: War Med., **1**, p. 205. **Doob, L. W.**: J. Abnor. and Soc. Psych., **36**, p. 2. **Larkey, S. V.**: War Med., **1**, p. 1. **Leland, R. G.**: Ibid., p. 1. Letters to Editor: Lancet, **1**, pp. 243, 261, 228, 261. **Maskin, M.**: Psychiatry, **4**, p. 97. **Sands, I. J.**: War Med., **1**, p. 203.

PHYSIOLOGY.

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF APRIL 15, 1941.

On the Phosphorylation Hypothesis of Glucose Absorption, With Special Reference to Phlorizin. LYLE VIBERT BECK (Department of Physiology, Hahnemann Medical College). The finding by Kalckar (Enzymologia, **2**, 47, 1937) that low concentrations of phlorizin inhibit the phosphorylation of hexoses by rabbit kidney brein has been confirmed. Phlorhizin also markedly inhibits the acid phosphatase of rat kidney cortex and intestinal mucosa, while having little effect on the corresponding alkaline phosphatases.

Combined barium precipitation—N.HCl hydrolysis experiments indicate that the increase in organic phosphate produced in the intestinal mucosa of rats by giving them glucose by stomach tube (*cf.* Laszt and Sullmann, Biochem. Ztschr., **278**, 401, 1935) is due to increase in concentration of a number of organic phosphate compounds. The considerable increase in the 0–7′ (minute) N.HCl fraction is apparently largely due to formation of adenylpyrophosphate, since this fraction was found mainly in the Ba precipitate fraction. Increases in the 7–180′ N.HCl fraction and in the difficultly hydrolyzable fraction (not hydrolyzed in 180′ by N.HCl) are due chiefly to formation of carbohydrate-phosphate compounds, since these fractions were found mainly in the Ba soluble fraction.

Using the method of Cori, Colowick and Cori (J. Biol. Chem., **121**, 465, 1937), no change in concentration of either glucose-1-PO_4 or phosphoglycerate in the intestinal mucosa was found on giving glucose. Under these same conditions an increase in concentration of compounds giving the Seliwanoff fructose reaction (Roe, J. Biol. Chem., **107**, 15, 1934) occurred.

M/50 phlorizin does not affect the increase in the 0–7′ N.HCl (pyrophosphate) fraction produced by 5.5% glucose, but definitely diminishes the increases otherwise produced in the 7–180′ fraction and in the difficultly hydrolyzable fraction (phosphoglyceric acid?). The increase in concentration of compounds giving the fructose reaction when glucose is given is diminished in the presence of M/50 phlorizin.

While the above findings may be interpreted as indicating that phosphorylation-dephosphorylation processes play a considerable rôle in glucose absorption, they indicate that if this is true the pathways involved are considerably more intricate than a simple phosphorylation and dephosphorylation of the glucose molecule.

The Effect of Brass Rings on Tissue Cultures of the Heart. M. J. Hogue (Department of Anatomy, University of Pennsylvania). Using a liquid medium which was a combination of Tyrode solution, Locke-Lewis solution and chick embryonic extract, tissue cultures of chick embryo heart, liver, lung, intestine, amnion and skeletal muscle were grown over brass rings sealed to glass slides with salvoline. The controls of the same tissues, in the same medium, were grown over glass depression slides. Further controls were grown in plasma and embryonic extract. The percentage of growth of fibroblasts from the different tissues showed great variations when grown over brass rings, the heart fibroblasts showed the least growth and the lung fibroblasts the most growth.

When good growths of heart fibroblasts were transferred from glass depression slides to slides with brass rings the fibroblasts soon died. Experiments with hypotonic solutions showed that death was not due to a change in the tonicity of the medium.

Since brass is an alloy of copper and zinc, small particles of copper and zinc were placed in the hollow of the depression slides and tissue cultures were inverted over them. Over the copper the fibroblasts grew well, but over the zinc there was little or no growth. Death of the fibroblasts over brass rings and over zinc particles was the same slow process. First there was the appearance of vacuoles around the nucleus, which became pyknotic, then the withdrawal of the cell processes and the contraction of the cell body while small clear blebs appeared over the surface of the cell. Cardiac muscle cells were not as sensitive to the zinc as the cardiac fibroblasts.

The Structure of Bacteria as Shown by the Electron Microscope. Stuart Mudd, T. F. Anderson, K. Polevitzky, and H. E. Morton (Department of Bacteriology, University of Pennsylvania). Micrographs of bacteria made with the RCA electron microscope have shown very definite differentiation between a solid outer cell wall and an inner fluid or potentially fluid protoplasm. In chains of *Strep. pyogenes* and of aërobic spore-bearing bacilli the continuity of the chain has been shown to be due essentially to the continuity of the outer cell walls. Division in a strain of *Strep. pyogenes* appears to be accomplished by a pinching off of the cell wall and its contained protoplasm. In species of the genus *Bacillus*, intercellular plates, as described by Knaysi and others, may be seen. Disruption of streptococci and bacilli by sonic vibration permits escape of the inner protoplasm, leaving the cell-walls as "ghosts."

Cells of *Mycobacterium tuberculosis* and *Corynebacterium diphtheriæ* have been relatively transparent to the electron beam. In tubercle bacilli opaque granular bodies of various sizes may be seen in the inner protoplasm. In diphtheria bacilli grown on blood agar, very striking polar granules are found. In diphtheria bacilli grown on potassium tellurite medium, needle-shaped crystals of metallic tellurium are clearly visible within the cell protoplasm. Shaking such bacterial cells with bromine water dissolves the crystals, a behavior which is to be expected with tellurium metal.

The Liver Glycogen and Lipid Concentration Following Diet and Intravenous Glucose Administration to the Dog and Man in the Presence of Common Duct Obstruction. I. S. Ravdin, H. M. Vars, Julius Schultz, Julian Johnson, and Elizabeth Thorogood (Harrison Department of Surgical Research, School of Medicine, University of Pennsylvania). It is generally believed that high concentrations of hepatic glycogen protect the liver from many hepatotoxic agents. Regardless of the validity of this impression, it is also widely believed that glucose administered intravenously is the best method of increasing hepatic glycogen. This is untenable except for brief periods of time, since it disregards the calorific requirements of man or animal. We have studied this in the dog in the presence of common duct obstruction.

During voluntary eating animals lost hepatic glycogen and increased liver lipid concentration. When in addition glucose was administered intravenously, the glycogen concentration was maintained and the liver lipid concentration was decreased. Where appetite was stimulated and the dogs also received glucose intravenously, the liver glycogen concentration increased by 84% and the lipid concentration decreased by 25%. Following forced feeding (88 calories per kilo of body weight per day) the liver glycogen concentration increased by 236% and the lipid concentration decreased by 73%. With only a 5% solution of glucose intravenously (50 cc. per kilo of body weight per day) the animal lost 50% of the original liver glycogen concentration.

In man similar data have been obtained. The data from man and dog suggest that if large accumulations of glycogen are desired, these must be obtained by the oral administration of foodstuffs, for such stores cannot be maintained unless the energy requirements are being met.

Notice to Contributors. Manuscripts intended for publication in the American Journal of the Medical Sciences, and correspondence, should be sent to the Editor, Dr. Edward B. Krumbhaar, School of Medicine, University of Pennsylvania, Philadelphia, Pa.

Articles are accepted for publication in the American Journal of the Medical Sciences exclusively.

All manuscripts should be typewritten on one side of the paper only, and should be double spaced with liberal margins. The author's chief position and, when possible, the Department from which the work is produced should be indicated in the subtitle. Illustrations accompanying articles should be numbered and have captions bearing corresponding numbers. For identification they should also have the author's name written on the margin. The recommendations of the American Medical Association Style Book should be followed. It is important that references should be numbered and at the end of the articles, arranged alphabetically according to the name of the first author and should be complete, that is, author's name, journal, volume, page and year (in Arabic numbers).

Return postage should accompany all manuscripts but will be returned to the author if the manuscript is accepted.

Two hundred and fifty reprints, with covers, are furnished gratis; additional reprints may be had in multiples of 250 at the expense of the author. They should be asked for when the galley proofs are returned.

Contributions in a foreign language, if found desirable for the Journal, will be translated at its expense.

Index photographed at the
beginning for the convenience
of the microfilm user.

Vo

POS
THE
BEE
HEB
SEA
THE
DIE
THE
PRO
THE
THE
LEU
ATR
TIB
THE
THE
FIB
ANI

COPYR

INDEX NUMBER

VOL. 201 NO. 6 JUNE, 1941 No. 831

Medical Library JUN 13 1941

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

REG. U. S. PAT. OFF.

E. B. KRUMBHAAR, M.D., EDITOR
RICHARD A. KERN, M.D., ASSISTANT EDITOR

ESTABLISHED 1820

POSSIBLE ADAPTATION TO A LOW VITAMIN B_1 INTAKE. By F. M. MEYERS, M.D. . . 785
THE RESPONSE OF BLOOD DONORS TO IRON. By ALBERT C. SANTY, M.D. . . . 790
BEE VENOM IN THE TREATMENT OF CHRONIC ARTHRITIS. By JOSEPH LEE HOLLANDER, M.D. . . . 796
HEBERDEN'S NODES. HEREDITY IN HYPERTROPHIC ARTHRITIS OF THE FINGER JOINTS. By ROBERT M. STECHER, M.D. . . . 801
SEASONAL VARIATION IN THE WATER CONTENT OF THE RESPIRATORY TRACT OF BIRDS AND MAMMALS. By ELDON M. BOYD, M.A., M.D., and G. M. JOHNSTON, M.A. . 810
THE EFFECT OF PHENOBARBITAL ON NORMAL AND IMPAIRED DEXTROSE TOLERANCE. By J. A. ROSENKRANTZ, M.D., and MAURICE BRUGER, M.D. . . . 815
DIETARY HYPERCHOLESTEROLEMIA. By ALFRED STEINER, M.D., and BEATRICE DOMANSKI, B.A. . . . 820
THE INCIDENCE OF CERTAIN SIGNS AND SYMPTOMS AT VARIOUS LEVELS OF BASAL AND TOTAL RESTING METABOLISM. AN ANALYSIS OF 1000 CASES. By J. J. SHORT, M.D., F.A.C.P. . . . 824
PROTHROMBIN STUDIES IN PULMONARY TUBERCULOSIS. By J. W. SAVACOOL, M.D. . 830
THE SURVIVAL TIME AFTER TRANSFUSION OF ERYTHROCYTES OF CITRATED HUMAN BLOOD STORED AT 4° TO 6° CENTIGRADE. By WILLIAM P. BELK, M.D., F.A.C.P., and B. C. BARNES, M.D. . . . 838
THE EFFECT OF GLUCOSE IN THE PRESERVATION OF CITRATED HUMAN BLOOD STORED AT 4° TO 6° CENTIGRADE. By WILLIAM P. BELK, M.D., F.A.C.P., and FLORENCE ROSENSTEIN, M.T. . . . 841
LEUKEMOID REACTIONS. By J. M. HILL, M.D., and C. N. DUNCAN, M.D. . . . 847
ATRIOVENTRICULAR NODAL RHYTHM. By NATHAN FLAXMAN, M.D. . . . 857
TIBIAL ARTERY CHANGES IN COMPARISON WITH THOSE OF THE RADIAL AND CORONARY ARTERIES. By S. W. SAPPINGTON, M.D., and J. ARTHUR HORNEFF, M.D. . 862
THE REACTIVITY OF INTRACRANIAL VESSELS IN THE AGED. By D. EWEN CAMERON, M.D., and S. R. ROSEN, M.D. . . . 871
THE EFFECT OF PREGNANCY UPON EXPERIMENTAL HYPERTENSION IN THE RABBIT. By JOHN D. CORBIT, JR., M.D. . . . 876
FIBRILLARY TWITCHINGS. AN INVESTIGATION OF THEIR SITE OF ORIGIN. By C. HUNTER SHELDEN, M.D., and HENRY W. WOLTMAN, M.D. . . . 884
ANIMAL EXPERIMENTS CONCERNING THE HORMONAL THERAPY OF TESTICULAR ATROPHY. By HANS SELYE, M.D., PH.D., and SYDNEY M. FRIEDMAN, M.D. . . 886

Contents continued on adv. page 10

LEA & FEBIGER
OWNERS AND PUBLISHERS
PHILADELPHIA

COPYRIGHT, 1941, BY LEA & FEBIGER. ALL RIGHTS RESERVED. ENTERED AT THE POST-OFFICE AT PHILADELPHIA AS SECOND-CLASS MATTER

PUBLISHED MONTHLY. SUBSCRIPTION, SIX DOLLARS A YEAR

TRIPLE ACTION

IN HYPERTENSION

For prompter and more lasting reduction of blood pressure, prescribe HEPVISC—the triple-action hypotensive.

1 **In a recent series of cases, blood pressure was reduced an average of 13 mm. Hg. after its administration.**

2 **Subjective symptoms of headache, dizziness and tinnitus were entirely cleared or definitely improved in more than 80% of instances.**

3 **Usually the hypotensive action of Hepvisc was prolonged many weeks.**

Hepvisc is a synergistic combination of Viscum album extract, desiccated liver, and desiccated insulin-free pancreas. All three ingredients are of recognized value as hypotensive agents.

When you prescribe Hepvisc to lower blood pressure, you avoid use of the nitrites and similar depressing drugs.

INDICATIONS: Essential hypertension, benign hyperpiesia, fibrotic kidney and hypertension accompanying pregnancy.

DOSAGE: 1 or 2 tablets three times daily, one-half hour before meals. Give in courses of two to three weeks with week's interval between. Supplied in bottles of 50 and 500 tablets.

Samples and literature to physicians on request.

HEPVISC

For Your Blood Pressure Cases

ANGLO-FRENCH DRUG CO. (U. S A.) INC., 75 VARICK ST., NEW YORK, N.Y

COMPACT

PORTABLE

QUIET

INTERNATIONAL MICRO CENTRIFUGE

For Semi-Micro and Micro Analysis

- Large capacity for student work—8 - 3 ml. or 5 ml. tubes.
- Quick starting—1780 r.p.m. in 15 seconds.
- Both *angle* and *horizontal* sedimentation and various combinations of both. (See illustration.)
- Carefully balanced for smooth operation.

Selling Price $35.00

INTERNATIONAL EQUIPMENT COMPANY

352 Western Avenue — ***Makers of Fine Centrifuges*** — Boston, Mass.

FOR SOME TYPES OF GASTRIC DISTRESS

Valentine's Meat Extract has long been used by the Medical Profession both here and abroad.

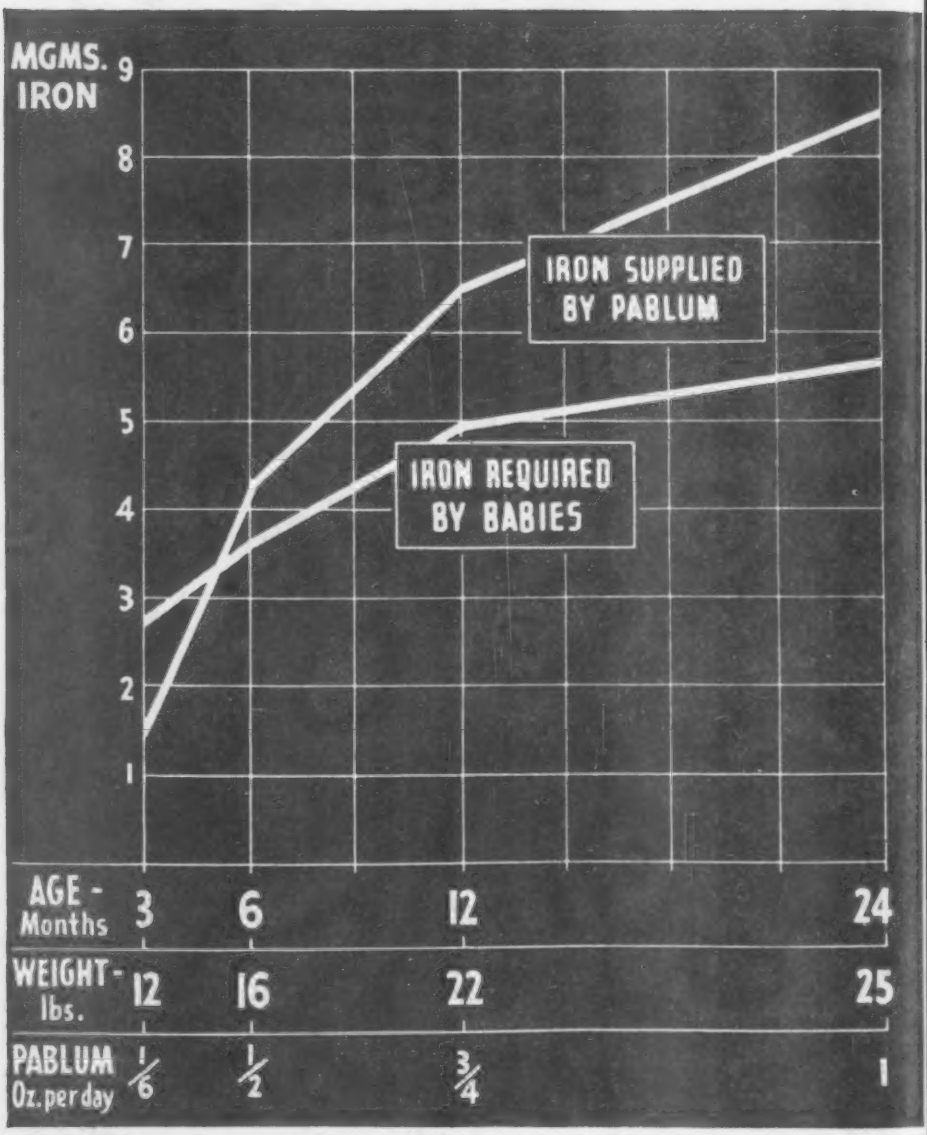
Recent physiological studies* indicate that meat extract, in therapeutic dosage, provides higher acid and pepsin concentrations of the stomach contents and inhibits intestinal regurgitation.

*Fisher and Apperly: J. Lab. Clin. Med., 26:823–27, 1941.

Reprints available upon request.

VALENTINE'S MEAT-JUICE COMPANY

RICHMOND, VIRGINIA



DAILY AMOUNT OF IRON REQUIRED BY NORMAL BABIES, AND AMOUNT SUPPLIED BY PABLUM

The infant starts life with a store of iron. There is a steady drain of this reserve during the first few months. Because both breast milk and cow's milk are poor in iron, it is becoming the practice to feed iron-bearing foods at as early an age as possible. As shown in the above chart, from about the fourth month Pablum alone supplies more than the infant's daily iron requirements. In this chart, the requirements are based on the conservative estimate of the Council on Foods, i.e., 0.5 milligram per kilogram of body weight. The iron supplied by Pablum is calculated on the basis of 8.5 mg. per ounce. On account of its thorough cooking Pablum is well tolerated, having been fed without gastrointestinal upset as early as the first month. Bibliography on request. Mead Johnson & Co., Evansville, Ind., U.S.A.